

Contact Network Epidemiology: Mathematical Methods of Modeling a Mutating Pathogen on a Two-type Network

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Chapter 1

Abstract

With the threat of diseases like Sudden Acute Respiratory Syndrome (SARS) and Avian Flu that can lead to global pandemics, it is important to be able to understand how diseases spread through a population and predict how many people will become infected. It is also important to learn how preventative treatments affect disease spread. Public health officials must prepare a different vaccine each year to deal with a different influenza strain. Furthermore, it is important to be able to determine how effective a particular vaccination strategy will be in the event of a limited vaccine supply.

The most common mathematical model of epidemic disease is based on the assumption that the population is homogenously mixed. That is, every member of the population is identical in how many other individuals he interacts with and every infected individual has the potential to spread disease to every other individual. However, these assumptions are unrealistic. To create a better model, the basic assumption of homogeneous mixing is removed. To do this, the population is modeled as a contact network. In a contact network, the population is represented by dots connected by lines. Each member is represented by a dot, or node, with disease-causing interactions between two members of a population represented by lines, or edges, between two nodes. This models the structure that exists in human populations by allowing individuals in a population to infect only a limited number of other individuals and allowing the number of contacts to vary between individuals.

Much is already understood about how network structure affects disease dynamics. This thesis uses the contact network model to study the impact of network structure on the dynamics of a mutating pathogen. By distributing the contacts within the population in different ways, the effect of the network's structure on the extent of the disease is observed. Given the distribution of contacts on the network and the probability that an individual

spreads the disease to a contact, the average sizes of a small outbreak (that which spreads to only a few people) and a large epidemic (that which spreads to a fixed proportion of the population, no matter the size) are calculated. These calculations are computed for different contact distributions and for a range of transmissibility values. Furthermore, these calculations are checked against simulations of the disease spreading over contact networks. This thesis also generalizes the contact network model to allow for both treated and untreated individuals in a population. In this generalization, not only does the number of contacts vary between individuals, but the probability of transmission also differs between treated and untreated individuals.

This thesis shows that the contact network model with pathogen evolution is similar to the basic model. It also shows that the predictions made by the model are supported by simulation in some cases but not in other. Furthermore, it shows a contact network model that incorporates two different kinds of nodes. Lastly, it shows that this new model reduces to the basic model under certain conditions.

Chapter 2

Introduction and Background

2.1 Introduction

The goal of this thesis is twofold. The first goal is to demonstrate the dynamics of a mutating pathogen on a contact network. The second is to model the spread of disease in a population in which some individuals have partial immunity through immunization or other prophylactic treatment. These two generalizations will later be joined together to study how treatment patterns on a contact network affect the spread and mutation of a disease.

This is an important goal because prophylactic treatment is a common form of disease prevention. Diseases such as malaria and avian influenza have treatments that confer at least partial immunity [Keller & Leder 2008]. However, diseases can mutate to avoid prophylactic treatments. Mutations in the genome of the influenza virus are the reason flu shots are recommended every year [CDC 2008].

Mathematical models of disease spread are useful because they can predict the average size of an epidemic given certain parameters. This model represents an improvement over previous models because it relaxes certain assumptions that are unrealistic. For years, the standard model of disease spread has been a compartmental or "SIR" model. In it, the population is divided into three compartments: Susceptible (S), Infected (I) and Removed (R). The dynamics of disease spread in this model are governed by a set of simple differential equations:

$$\begin{aligned}
\frac{dS(t)}{dt} &= -\gamma S(t)I(t) \\
\frac{dI(t)}{dt} &= \gamma S(t)I(t) - \beta I(t) \\
\frac{dR(t)}{dt} &= \beta I(t)
\end{aligned}$$

Where $S(t)$, $I(t)$, and $R(t)$ are proportions of the population that vary over time with

$$S(t) + I(t) + R(t) = 1.$$

The main parameter of this model is the basic reproductive number,

$$R_0 = \frac{\gamma}{\beta}.$$

The basic reproductive number indicates the average number of new cases that a infected individual will generate. This model predicts that an epidemic will occur if $R_0 > 1$. [Kermack & McKendrick 1927]

However, this model assumes that the population is "fully mixed." That is, any member of the population can come into contact with any other member of the population and the probability of coming into contact with any member of the population is the same.

Newer models of disease spread [Newman 2002] relax the assumption of a typical SIR model that a population is fully mixed and replaces it with a contact network model. A *contact network* is a model of a population that considers the interactions between individuals. Instead of assuming that a susceptible individual can come into contact with any individual in the population, the contact network model assumes each individual only has a certain number of contacts. The contact network can be thought of as a graph with the vertices representing people and the edges representing contacts. In this model, any potentially disease-causing interaction is considered a contact. Thus, a contact network for a sexually-transmitted disease like gonorrhea will be very different than the contact network of a disease like the flu that can be spread through the air.

The contact network model of disease spread has advantages over models that assume the population to be fully mixed. For one, it does not assume that every individual has the same contact pattern like the SIR model does. This limitation was especially notable in the case of the SARS virus. In this example, epidemiologists predicted a reproductive number R_0 between 2.2 and 3.6. [Lipsitch et al. 2003] However, an epidemic did not result. A few

of the SARS patients were classified as *super spreaders*, that is they were responsible for causing at least 10 infections. [Leo et al. 2003] Clearly, the heterogeneity of the contact network must be considered in this case. The contact network model also allows for other differences in contact patterns like directed contacts. For example, if an individual is infected with a disease, he may go to a doctor to treat it. However, if a doctor gets sick he will not seek out his patients. You can account for this in a contact network using directed edges [Meyers 2006].

2.2 Probability Generating Functions

In his paper, Newman represents the distribution of degrees in a network as a *probability generating function* (pgf). A pgf, generally written as

$$\begin{aligned} G_0(x) &= \sum_{k=0}^{\infty} p_k x^k \\ &= p_0 + p_1 x^1 + p_2 x^2 + \dots \end{aligned}$$

is a useful mathematical tool that encapsulates all of the important information of a probability distribution within a polynomial. In a pgf, the coefficient of the x^k term, p_k , represents the probability that a random variable with a probability distribution given by G_0 will have value k . For example, a binomial distribution, which gives the probability of k successes in n independent trials of an experiment each with probability of success p (i.e. k heads in n coin tosses) has probability

$$p_k = \binom{n}{k} p^k (1-p)^{n-k}.$$

So the generating function $F(x)$ for this probability distribution, known as the binomial distribution, is given by

$$\begin{aligned} F(x) = \sum_{k=0}^n p_k x^k &= \sum_{k=0}^n \binom{n}{k} p^k (1-p)^{n-k} x^k \\ &= (1-p)^n + \binom{n}{1} (1-p)^{n-1} p x + \dots + p^n x^n \\ &= (1-p + p x)^n \end{aligned}$$

In the case of our degree distribution, p_k represents the proportion of the nodes in the network with k vertices.

True to its name, a probability generating function is useful for finding individual probabilities of a distribution. Given a pgf $G(x)$, the probability p_k can be computed by

$$p_k = \frac{1}{k!} \left. \frac{d^k G(x)}{dx^k} \right|_{x=0}$$

By the axioms of probability, we also know that for a properly normalized distribution,

$$\sum_{k=0}^{\infty} p_k = 1.$$

Furthermore, we can compute the *mean degree* ($\langle k \rangle$), or average number of vertices emanating from a node of the distribution, as follows:

$$z = \langle k \rangle = \left. \frac{dG}{dx} \right|_{x=1} = \sum_{k=0}^{\infty} k p_k.$$

Other moments can also be computed using $G(x)$, namely

$$\langle k^n \rangle = \frac{1}{n!} \left[\frac{d^n}{dx^n} x^n G(x) \right]_{x=1} = \sum_{k=0}^{\infty} k^n p_k.$$

In this thesis, we will consider three degree distributions: Poisson, exponential and scale-free. For a given mean λ , the three distributions indicate the proportion of edges with degree k will be:

$$p_k = \frac{e^{-\lambda} \lambda^k}{k!} \text{ (Poisson)}$$

$$p_k = (1 - e^{-\frac{1}{\lambda}}) e^{-\frac{k}{\lambda}} \text{ (Exponential)}$$

$$p_k = \frac{k^{-\gamma}}{\zeta(\gamma)} \text{ (Scale-free)}$$

where γ is found for a given λ by numerically solving the following equation for γ :

$$\lambda = \sum_{k=0}^{\infty} k p_k = \sum_{k=0}^{\infty} \frac{k^{1-\gamma}}{\zeta(\gamma)}$$

and $\zeta(\gamma)$ is the Riemann Zeta function given by

$$\zeta(\gamma) = \sum_{k=1}^{\infty} \frac{1}{k^{\gamma}}.$$

We consider these distributions because they differ in variance; for a given mean λ , the Poisson distribution has the smallest variance, λ , and the exponential distribution has variance λ^2 . On the other hand, the variance of the Scale-free network is $+\infty$. Variance for a random variable k is defined as

$$\langle k^2 \rangle - (\langle k \rangle)^2.$$

However, for the Scale-free network,

$$\langle k^2 \rangle = \sum_{k=0}^{\infty} k^{2-\gamma}.$$

Because the value of γ ranges between 1 and 3, $(2 - \gamma)$ ranges between -1 and 1. Thus, the second moment, $\langle k^2 \rangle$, diverges because

$$\sum_{k=0}^{\infty} k^{-p}$$

only converges for $p > 1$. So, because $\langle k^2 \rangle$ diverges for the scale-free network, the variance diverges. In the context of contact networks, the difference in variances means that a Poisson contact network has many nodes with number of vertices close to the mean, while the scale-free network has a few nodes with a high number of vertices and a lot of nodes with very few vertices - a so-called "hub and spoke" model. The fact that the scale-free network's variance does not converge also means that the probability of a node in the network having a very high degree is much greater than the same probability for a node in one of the other networks. The exponential network lies in between these two.

These facts are illustrated by Figure 2.1, a graph showing the probability that, for a given k , a node has degree greater than k for each of the three distributions with a mean $\lambda = 5$. One can see that most nodes in the Poisson network have degree close to the mean 5 because the graph drops precipitously at $k = 1$ and is near 0 when $k = 10$. On the other hand, the graph of the scale-free network drops very quickly between $k = 1$ and $k = 3$ but then slowly decreases towards 0. This indicates that the scale-free network has a high number of nodes with low degree, but also some with much higher degree.

2.3 Disease Transmission

The only parameter in the contact network model of disease transmission is the probability that an infected individual will transmit the disease to one of

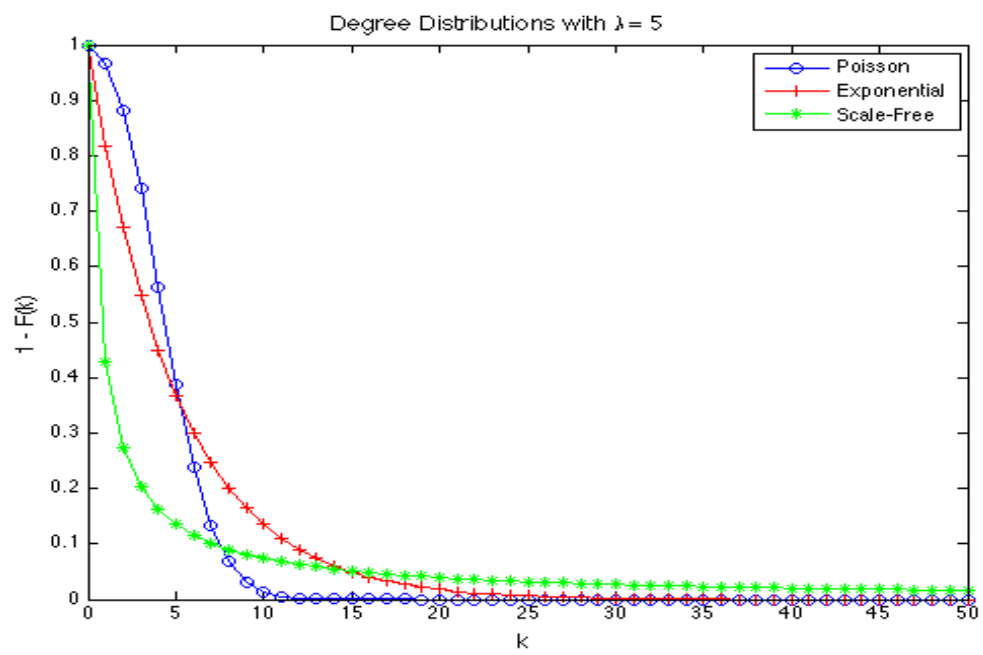


Figure 2.1: The three degree distributions with mean $\lambda = 5$ illustrated as upper-tails.

his (or her) contacts, this value is known as the *transmissibility*. The transmissibility value can vary for each contact, so the probability of individual i infecting individual j is denoted T_{ij} . To find T_{ij} , we first consider r_{ij} , the probability that the infected individual i will infect individual j in one time step. The probability that this event does not happen is the $1 - r_{ij}$. If i remains infectious for τ time steps, then the probability of transmission is then one minus the probability that i does not infect j during any of the τ time steps. Thus,

$$T_{ij} = 1 - (1 - r_{ij})^\tau.$$

An independent and identically distributed set of random variables (iid) is one in which each random variable has the same probability distribution but each variable is independent of any other. The set $\{r_{ij}\}_{i,j \in \mathbf{N}}$ is assumed to be iid, so T_{ij} is also an iid random variable and we can work with the mean transmissibility:

$$T = \langle T_{ij} \rangle = 1 - \int_0^\infty [1 - P(r)(1 - r)^\tau] dr$$

where $P(r)$ is the probability density function for the distribution of r_{ij} . The fact that we can work with the average value T allows the model to be much more tractable than it would otherwise be.

When considering the spread of disease over a network, it is important to consider the number of contacts an individual has once he or she becomes infected. The individual cannot spread the disease back to the individual who infected her, so the size of the outbreak depends on how many people she can infect. Thus, it is important to consider the excess degree distribution of the network - the distribution of the number of other edges at a node found by following a randomly chosen edge. Nodes of higher degree will be more likely to lie at the end of a randomly chosen edge, so the probability of having excess degree $k - 1$ is proportional to kp_k . Thus, the degree distribution is

$$G_1(x) = \frac{\sum_{k=0}^\infty kp_k x^{k-1}}{\sum_{k=0}^\infty kp_k} = \frac{1}{z} \sum_{k=0}^\infty kp_k x^{k-1}$$

To introduce disease onto the network, consider the probability that a node with k edges transmits the disease to exactly m of its contacts. If T is the transmissibility, the probability is

$$\binom{k}{m} T^m (1 - T)^{k-m}.$$

Nodes that are infected by the disease are referred to as *occupied*. The generating function for the distribution of occupied edges is

$$\begin{aligned}
G_0(x; T) &= \sum_{m=0}^{\infty} \sum_{k=m}^{\infty} p_k \binom{k}{m} T^m (1-T)^{k-m} x^m \\
&= \sum_{k=0}^{\infty} p_k \sum_{m=0}^k \binom{k}{m} (Tx)^m (1-T)^{k-m} \\
&= \sum_{k=0}^{\infty} p_k (1 + (x-1)T)^k \\
&= G_0(1 + (x-1)T).
\end{aligned}$$

A similar calculation can be performed to derive the generating function for excess occupied edges:

$$G_1(x; T) = G_1(1 + (x-1)T)$$

These pgfs have interesting properties for certain values of x and T :

$$G_0(1; T) = G_0(1) = 1,$$

which indicates that $G_0(x; T)$ is still a properly normalized pgf;

$$G_0(x; 1) = G_0(x),$$

which shows that if the probability of transmission is 1, the generating function of the disease is the same as the generating function for the network and thus all nodes will become infected; and finally

$$G'_0(1; T) = T G'_0(1),$$

which shows that the mean occupied degree of the network of occupied is just the mean degree of the contact network, $G'_0(1)$, multiplied by the probability of infection, T .

2.4 Predicting Epidemic Size

The purpose of deriving these equations is to determine the disease's extent over the network. To do this, first consider the probability generating function

$$H_1(x; T) = \sum_{s=0}^{\infty} Q_s(T) x^s$$

of the the size of a cluster of infected nodes emanating from a given edge. In this pgf, $Q_s(T)$ represents the probability (given the transmissibility T) that transmission of the disease along one edge will result in an epidemic cluster of size s . When the disease travels along the edge to a node, it becomes infected and it can then spread infection via each of its excess edges. So we multiply x (representing the first infected node) by the excess degree distribution $G_1(x; T)$. However, each edge that the infection spreads along creates a whole new cluster of infected edges and $G_1(x; T)$ only represents the number of excess edges emanating from a node. Therefore, the argument of G_1 is not x , but $H_1(x; T)$, the size of the cluster of infected edges emanating for each of the infected edges. Thus, $H_1(x; T)$ is recursive:

$$H_1(x; T) = xG_1(H_1(x; T); T)$$

Next, consider the probability generating function of the size of a cluster of infected nodes resulting from a single infected node:

$$H_0(x; T) = \sum_{s=0}^{\infty} P_s(T)x^s$$

Similarly to $Q_s(T)$, $P_s(T)$ is the probability (given T) that a single infected node will result in an outbreak of size s . To derive $H_0(x; T)$, we multiply x , representing the initial infected node, by the degree distribution, $G_0(x; T)$ (not the excess degree because the disease has not spread along any edges yet). However, the argument of $G_0(x; T)$ must be adjusted again to account for the size of the epidemic along each of the initial node's vertices. But, as we found above, the size of the outbreak from a given vertex is distributed by $H_1(x; T)$. So we have

$$H_0(x; T) = xG_0(H_1(x; T); T)$$

From these equations we can solve for the average number of people, $\langle s \rangle$, that will be infected by the disease.

$$\begin{aligned} \langle s \rangle &= \sum_{s=0}^{\infty} sP_s(T) \\ &= H'_0(1; T) \\ &= G_0(H_1(1; T); T) + (1)G'_0(H_1(1; T); T)H'_1(1; T) \end{aligned}$$

However, because G_0 and H_1 are properly normalized,

$$G_0(1; T) = H_1(1; T) = 1.$$

Thus,

$$\langle s \rangle = 1 + G_0(1; T)H'_1(1; T).$$

Then,

$$H'_1(x; T) = G_1(H_1(x; T); T) + xG'_1(H_1(x; T); T)H'_1(x; T).$$

So,

$$H'_1(1; T) = 1 + G'_1(1; T)H'_1(1; T).$$

Solving for $H'_1(1; T)$ yields

$$H'_1(1; T) = \frac{1}{1 - G'_1(1; T)}$$

Therefore,

$$\begin{aligned} \langle s \rangle &= 1 + G'_0(1; T)H'_1(1; T). \\ &= 1 + G'_0(1; T) \left(\frac{1}{1 - G'_1(1; T)} \right) \\ &= 1 + \frac{TG'_0(1)}{1 - TG'_1(1)} \end{aligned}$$

However, this only applies for certain transmissibility values. As T approaches $\frac{1}{G'_1(1)}$, the denominator of the expression for $\langle s \rangle$ becomes very small and thus $\langle s \rangle$ approaches ∞ . Thus,

$$T_c = \frac{1}{G'_1(1)}$$

is known as the *critical transmissibility*. Referring back to the compartmental model, R_0 was defined as the average number of new infections that an infected individual would produce. In the contact network model, this is simply the average number of occupied edges emanating from an infected edge. Thus,

$$R_0 = G'_1(1; T) = TG'_1(1)$$

Thus when $R_0 = 1, T = \frac{1}{G'_1(1)}$. This is our critical transmissibility value T_c . Recall that when $R_0 > 1$, an epidemic will occur. This happens when $T > T_c$. Because, $H_0(x; T)$ is the generating function for the size of small outbreaks,

$$H_0(1; T) = \sum_{k=0}^{\infty} P_s(T)$$

is the probability of a small outbreak occurring. Thus, the probability of a large outbreak is given by

$$S(T) = 1 - H_0(1; T) = 1 - G_0(H_1(1; T); T).$$

However,

$$H_1(1; T) = G_1(H_1(1; T); T)$$

So

$$S(T) = 1 - G_0(u; T),$$

where u is the solution to

$$u = G_1(u; T).$$

In practice, u can be solved for numerically. In this case, $S(T)$ represents the size of the epidemic as well as its probability.

2.5 Effect of network structure on disease spread

The values of $\langle s \rangle$ and $S(T)$ can be computed for the three types of networks we consider (Poisson, exponential, scale-free) over the range of transmissibility values ($0 \leq T \leq 1$) to show the behavior of the epidemic as T changes. In the first figure, we can see the value of $\langle s \rangle$ for each distribution diverge as T approaches the respective T_c values. We can also see how the values of T_c and $S(T)$ differ for the different distributions. The following table shows T_c for the three types of networks with mean $\lambda = 5$.

Network Type	T_c
Poisson	.1922
Exponential	.1263
Scale-free	.0153

Figure 2.2 shows how $\langle s \rangle$, the expected number of infected individuals below the critical transmissibility T_c grows as the transmissibility T grows. The graph also demonstrates how the predicted number of infections, $\langle s \rangle$, goes to infinity as T approaches T_c . Above this range of transmissibility values, the expected proportion of the population infected is shown in Figure 2.3. In this case, the expected proportion of the population infected is the same as the probability of an epidemic occurring. The figures also allow us to observe the differences in disease dynamics between the different networks. The Scale-free network has a very low T_c value compared to the other network types. This is because once the disease spreads to a "hub",

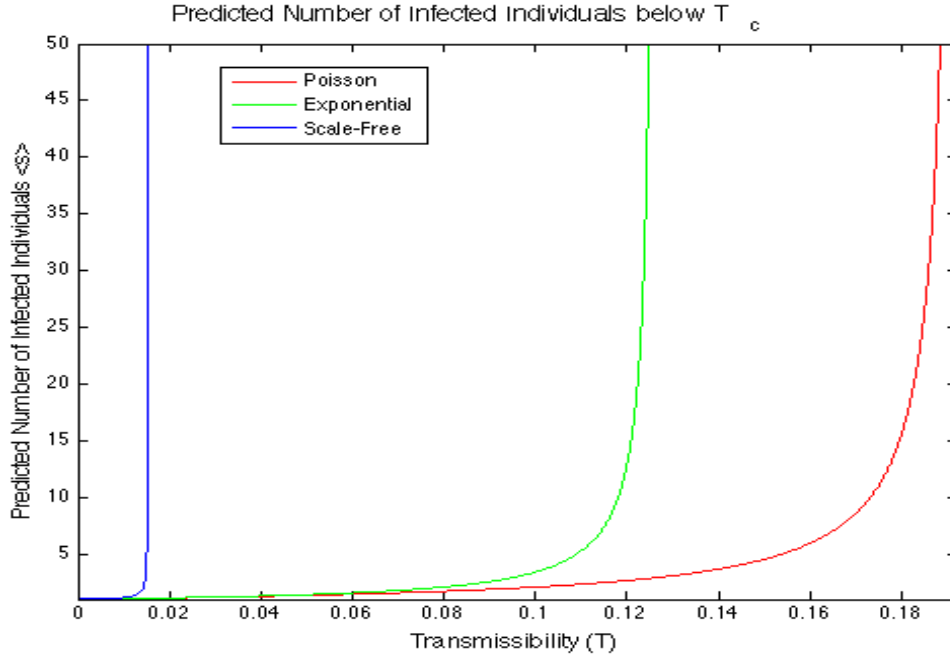


Figure 2.2: Predicted Number of Infected Individuals below T_c

many infections will result because that hub has a high excess degree. The networks with lower variances have a much higher T_c value because the average excess degree for these networks is much lower. However, the proportion of infected individuals for a given transmissibility is lower in networks with high degree variance because the failure to infect a single node can cut off a large portion of the network. This is not the case for the Poisson network because the contacts are more evenly distributed.

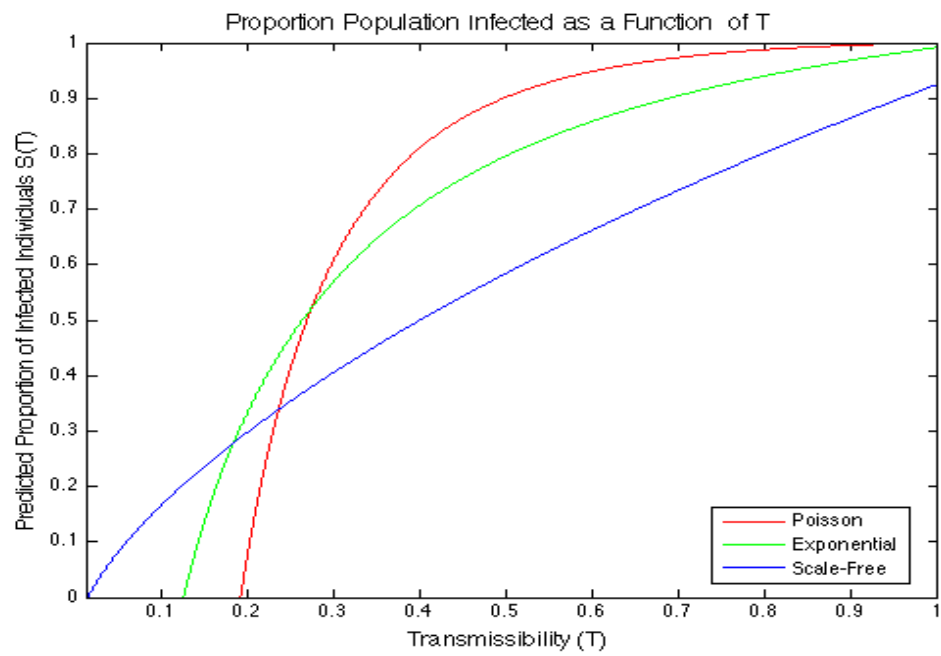


Figure 2.3: Predicted Proportion of Population Infected above T_c

Chapter 3

Methods

As mentioned before, this thesis consists of two projects. The first is to study a contact network model of the spread of a mutating pathogen. The second is to develop a model for disease spread over a two-type network. The different parts require different methods to complete. To look at the dynamics of the mutating disease, we use the derivations by Shweta Bansal in her paper (in preparation) “A Network Model with Pathogen Evolution” [Bansal & Meyers, 2008] to look at the extent of disease spread for a range of transmissibility values. We then use simulation to try to verify these values. The other results of this thesis, the analytic calculation of the extent of disease spread in a network with two types of nodes, uses the standard techniques of probability theory and calculus, and thus will only be discussed in the results section.

3.1 Spread of a Mutating Disease

In her paper, Shweta Bansal generalizes the contact network model of disease spread to allow for the evolution of the pathogen. The model begins with an individual infected with the *wild-type*, or commonly occurring, virus that can spread with probability T , but there is then a probability μ that the wild-type virus will mutate into a *mutant* virus. That is, an individual infected with the wild-type virus will transmit the wild-type virus with probability $T(1 - \mu)$ and the mutant virus with probability $T\mu$. The wild-type and mutant strains are the only two genotypes, and the mutant virus cannot mutate back to the wild-type virus, so an individual with the mutant virus will spread the mutant disease to a contact with probability T_μ . Below are the derivations for the sizes of disease clusters and the probabilities of large-scale epidemics.

3.1.1 Generating Functions

As with the contact network model of disease transmission discussed in the background, this mode begins with the probability generation function for the network, $G_0(x)$. Because this model makes the same assumptions about the contact network as the previous model, there are many key similarities between the two, thus this PGF has the same properties as the PGF for the previous model. Most notably, it also has an excess degree distribution

$$G_1(x) = \frac{\sum_{k=0}^{\infty} k p_k x^{k-1}}{\sum_{k=0}^{\infty} k p_k} = \frac{1}{\langle k \rangle} \sum_{k=0}^{\infty} k p_k x^{k-1}$$

The first difference appears when we consider disease transmission, namely the PGFs for occupied edges. In this model, there are two: the generating function for the number of occupied edges connecting to an individual with the wild-type virus, $G_0^W(x, y; T, \mu)$, and the generating function for the number of occupied edges connecting to an individual with the mutated virus, $G_0^M(y; T_\mu)$. Furthermore, these PGFs discern between edges connected to an individual with the wild-type virus, and to individuals with the mutant virus. So, to create the probability generating function for the distribution of occupied edges connected to an individual infected with the wild-type virus consider the probability that, given the parameters T , T_μ and μ , such an individual with k contacts will spread the virus to $a + b$ total individuals with b mutations. The probability of this is:

$$\binom{k}{a, b} (T(1 - \mu))^a (T_\mu)^b (1 - T)^{k-(a+b)}$$

Notice that this reduces to the Newman model when $b = 0$ and $\mu = 0$. Thus, for the probability generating function for occupied edges connected to an individual infected with the wild-type strain is:

$$\begin{aligned} G_0^W(x, y; T, \mu) &= \sum_{a=0}^{\infty} \sum_{b=0}^{\infty} \left[\sum_{k=a+b}^{\infty} p_k \binom{k}{a, b} (T(1 - \mu))^a (T_\mu)^b (1 - T)^{k-(a+b)} \right] x^a y^b \\ &= \sum_{k=0}^{\infty} \left[\sum_{a=0}^k \sum_{b=0}^{k-a} \binom{k}{a, b} (T(1 - \mu)x)^a (T_\mu y)^b (1 - T)^{k-(a+b)} \right] \\ &= \sum_{k=0}^{\infty} [p_k (1 - T + T(1 - \mu)x + T_\mu y)^k] \\ &= G_0(1 - T + T(1 - \mu)x + T_\mu y) \end{aligned}$$

where x corresponds to edges leading to an individual infected with the wild-type strain and y corresponds to edges leading to an individual infected with the mutant strain.

The PGF for the occupied edges emanating from an individual infected with the mutant strain is

$$\begin{aligned}
G_0^M(y; T_\mu) &= \sum_{a=0}^{\infty} \left[\sum_{k=a}^{\infty} p_k \binom{k}{a} (T_\mu)^a (1 - T_\mu)^{k-a} \right] y^a \\
&= \sum_{k=0}^{\infty} p_k \left[\sum_{a=0}^k \binom{k}{a} (T_\mu y)^a (1 - T_\mu)^{k-a} \right] \\
&= \sum_{k=0}^{\infty} p_k (1 - T_\mu + T_\mu y)^k \\
&= G_0(1 - T_\mu + T_\mu y).
\end{aligned}$$

Similar to the basic model, these occupied edge distributions have their excess occupied edge counterparts:

$$G_1^W(x, y; T, \mu) = G_1(1 - T + T(1 - \mu)x + T\mu y) \text{ and } G_1^M(y; T_\mu) = G_1(1 - T_\mu + T_\mu y)$$

These PGFs have important properties. First,

$$G_0^W(x, y; 1, \mu) = G_0((1 - \mu)x + \mu y),$$

meaning that if the probability of transmitting the wild-type virus is 1, all edges connected to a wild-type node will be infected. Furthermore, the proportion of edges occupied by the wild-type virus will be $1 - \mu$ and the proportion of edges occupied by the mutant virus will be μ . Similarly,

$$G_0^M(y; 1) = G_0(y).$$

Thus, if $T_\mu = 1$ then all edges connected to a mutant-infected node will be occupied by the mutant virus. Furthermore, because

$$G_0^W(1, 1; T, \mu) = G_0(1) = 1$$

and

$$G_0^M(1; T_\mu) = G_0(1) = 1$$

both G_0^W and G_0^M are properly normalized PGFs. Next, the number of edges occupied by the wild-type virus is given by:

$$\left. \frac{\partial G_0^W}{\partial x} \right|_{x=1, y=1} = G_0'(1)T(1 - \mu).$$

So the average number of edges occupied by the wild-type virus is equal to the average number of contacts for a node, $G'_0(1)$, times the proportion that would be infected by the wild-type virus, $T(1 - \mu)$. Similarly,

$$\left. \frac{\partial G_0^W}{\partial y} \right|_{x=1, y=1} = G'_0(1)T\mu.$$

So the average number of edges emanating from a wild-type node occupied by the mutant virus is equal to the average number of contacts for a node, $G'_0(1)$, times the probability of a wild-type individual transmitting the mutant virus, $T\mu$. Finally,

$$\left. \frac{dG_0^M(y; T_\mu)}{dy} \right|_{x=1} = G'_0(1)T\mu.$$

This shows that expected number of occupied edges emanating from a mutant individual is equal to the expected number of edges, $G'_0(1)$ times the probability transmitting the mutant disease, T_μ . The same properties hold for the excess occupied degree distributions.

$$\left. \frac{\partial G_1^W(x, y; T, \mu)}{\partial x} \right|_{x=1, y=1} = T(1 - \mu)G'_1(1)$$

$$\left. \frac{\partial G_1^W(x, y; T, \mu)}{\partial y} \right|_{x=1, y=1} = T\mu G'_1(1)$$

and

$$\left. \frac{dG_1^M(y; T_\mu)}{dy} \right|_{y=1} = T_\mu G'_1(1)$$

This tells us the expected excess occupied degree for a given node type (wild-type or mutant) and edge type (wild-type or mutant) is the expected excess degree for a node times the probability of that node transmitting a given type of infection.

3.1.2 Distribution of Outbreak Size

As with the basic model, the next step is to determine the size of an epidemic cluster attached to a randomly chosen, wild-type infected node. Define the following probability generating functions for the distribution of such sizes:

$$H_0^W(x; T, \mu) = \sum_{s=0}^{\infty} P_s(T, \mu)x^s$$

for the size of a cluster of individuals infected with the wild-type virus, and

$$H_0^M(y; T, \mu, T_\mu) = \sum_{s=0}^{\infty} Q_s(T, \mu, T_\mu) y^s$$

for the size of a cluster of individuals infected with the mutant virus. However, to determine the size of an epidemic, we must first define the PGFs for the size of an outbreak from a randomly chosen edge:

$$H_1^W(x; T, \mu) = \sum_{t=0}^{\infty} P_t(T, \mu) x^t$$

is the generating function for the size of a wild-type cluster beginning at a random edge occupied by the wild-type strain and

$$H_1^M(y; T, \mu, T_\mu) = \sum_{t=0}^{\infty} Q_t(T, \mu, T_\mu) y^t$$

is the the generating function for the size of a mutant cluster beginning at a random edge occupied by the wild-type strain.

To find H_1^W , we follow that random occupied edge to the node infected with the wild-type strain, which gives us x , then we must account for the edges of that node occupied by the wild-type strain. Thus, we multiply by the excess degree distribution for a wild-type node, $G_1^W(x, y; T, \mu)$. However, each of those occupied edges will lead to more infections, so the first argument of G_1^W , which counts the excess, occupied wild-type edges of the node is $H_1^W(x; T, \mu)$. Because H_1^W only counts wild-type infections, the second argument is 1. This gives us

$$H_1^W(x; T, \mu) = x G_1^W(H_1^W(x; T, \mu), 1; T, \mu).$$

The process is similar to find H_1^M . Follow a random edge occupied by the wild-type strain to the infected node. This node is not counted because we are only concerned with mutant infections, however this individual has the potential to infect some of his/her neighbors with the mutant strain as do the contacts that he/she infects with the wild-type strain. Thus, H_1^M is given by the wild-type excess occupied degree PGF, $G_1^M(x, y; T, \mu)$ with arguments $H_1^M(x; T, \mu)$ to account for its edges occupied by the wild-type strain that go one to produce mutant infections and $\Gamma_1^M(x; T_\mu)$, the PGF for the infected cluster attached to a randomly chosen edge occupied by the mutant strain. Thus,

$$H_1^M(y; T, \mu, T_\mu) = G_1^W(H_1^M(y; T, \mu, T_\mu), \Gamma_1^M(y; T_\mu); T, \mu, T_\mu)$$

It is next necessary to find Γ_1^M . Following a random edge occupied by the mutant strain leads to a node infected by the mutant strain, which gives x , this node then leads to infections along the edges given by the mutant excess occupied degree distribution $G_1^M(x; T_\mu)$. However, it is then necessary to account for the size of the clusters attached to these edges. This is given by Γ_1^M . Therefore, we have the self-consistent equation

$$\Gamma_1^M(x; T_\mu) = xG_1^M(\Gamma_1^M(x; T_\mu); T_\mu).$$

We can now define $H_0^W(x; T, \mu)$ and $H_0^M(y; T_\mu)$, the generating functions for the sizes of outbreaks emanating from a wild-type node and mutant node, respectively, in terms of $H_1^W(x; T, \mu)$ and $H_1^M(y; T_\mu)$, the generating functions for cluster sizes starting from a randomly chosen wild-type infected vertex. To do this for H_0^W , start with a randomly chosen vertex infected with the wild-type strain, x , then count all of its edges occupied by the wild-type infection, given by $G_0^W(x, y; T, \mu)$. Lastly, account for the size of the clusters attached to those edges by replacing the first argument of G_0^W with $H_1^W(x; T, \mu)$. Thus,

$$H_0^W(x; T, \mu) = xG_0^W(H_1^W(x; T, \mu), 1; T, \mu)$$

Similarly,

$$H_0^M(y; T, \mu, T_\mu) = G_0^W(H_1^M(y; T_\mu), \Gamma_1^M(y; T_\mu); T, \mu, T_\mu)$$

3.1.3 Calculating Outbreak Size

To find the expected size of an outbreak, we differentiate $H_0^W(; T, \mu)$ and $H_0^M(x; T_\mu)$ with respect to x and evaluate at 1. This gives

$$\begin{aligned} \langle s_w \rangle &= \left. \frac{dH_0^W(x; T, \mu)}{dx} \right|_{x=1} \\ &= G_0^W(H_1^W(1; T, \mu), 1; T, \mu) \\ &\quad + \left. \frac{\partial G_0^W(H_1^W(x; T, \mu), 1; T, \mu)}{\partial x} \right|_{x=1} \left. \frac{dH_1^W(x; T, \mu)}{dx} \right|_{x=1} \\ &= 1 + G_0'(1)T(1 - \mu) \left. \frac{dH_1^W(x; T, \mu)}{dx} \right|_{x=1} \end{aligned}$$

and

$$\begin{aligned}
\langle s_m \rangle &= \left. \frac{dH_0^M(y; T_\mu)}{dy} \right|_{y=1} \\
&= \left. \frac{\partial G_0^W(H_1^M(y; T_\mu), \Gamma_1^M(y; T_\mu); T_\mu)}{\partial x} \right|_{y=1} \left. \frac{dH_1^M(y; T_\mu)}{dy} \right|_{y=1} \\
&\quad + \left. \frac{\partial G_0^W(H_1^M(y; T_\mu), \Gamma_1^M(y; T_\mu); T_\mu)}{\partial y} \right|_{y=1} \left. \frac{d\Gamma_1^M(y; T_\mu)}{dy} \right|_{y=1} \\
&= \left. \frac{\partial G_0^W(x, y; T_\mu)}{\partial x} \right|_{x=1, y=1} \left. \frac{dH_1^M(y; T_\mu)}{dy} \right|_{y=1} \\
&\quad + \left. \frac{\partial G_0^W(x, y; T_\mu)}{\partial y} \right|_{x=1, y=1} \left. \frac{d\Gamma_1^M(y; T_\mu)}{dy} \right|_{y=1} \\
&= G'_1(1)T(1-\mu) \left. \frac{dH_1^M(y; T_\mu)}{dy} \right|_{y=1} + G'_1(1)T\mu \left. \frac{d\Gamma_1^M(y; T_\mu)}{dy} \right|_{y=1}
\end{aligned}$$

Then, deriving, we get

$$\begin{aligned}
\left. \frac{dH_1^W(x; T, \mu)}{dx} \right|_{x=1} &= \frac{1}{1 - G'_1(1)T(1-\mu)} \\
\left. \frac{dH_1^M(y; T_\mu)}{dy} \right|_{y=1} &= \frac{G'_1(1)T(1-\mu)}{(1 - G'_1(1)T_\mu)(1 - G'_1(1)(1-\mu))}
\end{aligned}$$

and

$$\left. \frac{d\Gamma_1^M(y; T_\mu)}{dy} \right|_{y=1} = \frac{1}{1 - G'_1(1)T_\mu}.$$

[See Appendix A for full derivations]

Thus,

$$\langle s_w \rangle = 1 + \frac{G'_0(1)T(1-\mu)}{1 - G'_1(1)T(1-\mu)}$$

and

$$\langle s_m \rangle = \frac{G'_0(1)G'_1(1)T^2(1-\mu)^2}{(1 - G'_1(1)T_\mu)(1 - G'_1(1)T(1-\mu))} + \frac{G'_1(1)T}{1 - G'_1(1)T_\mu}$$

As you can see, these equations have critical transmissibility values above which the equations are no longer valid. For $\langle s_w \rangle$ we have

$$T^c = \frac{1}{G'_1(1)(1-\mu)}.$$

When $T = T^c$, the denominator of $\langle s_w \rangle$ is 0. This is the critical transmissibility value for the wild-type pathogen. We also have

$$T_\mu^c = \frac{1}{G'_1(1)}$$

as the critical transmissibility for s_m . However, T^c is also a critical transmissibility value for $\langle s_m \rangle$. As with Newman's model, we consider the number of new infections, both wild-type and mutant, generated from an infected individual. The number of new wild-type infections generated from a wild-type individual, R_0^w , is found by multiply the average number of contacts, $G'_0(1)$ by the probability of transmitting the wild-type infection, $T(1 - \mu)$. Similarly, the number of mutant infections generated by an individual with the mutant virus is the average number of contacts, $G'_0(1)$, multiplied by the probability of transmitting the mutant virus, T_μ . When the average number of people infected by an infected individual exceeds 1, an epidemic will occur, so:

$$R_0^w = G'_0(1)T(1 - \mu) = 1$$

occurs when

$$T = \frac{1}{G'_0(1)(1 - \mu)}.$$

Similiarly,

$$R_0^m = G'_0(1)T_\mu = 1$$

occurs when

$$T_\mu = \frac{1}{G'_0(1)}.$$

These are precisely our critical transmissibility values T^c and T_μ^c .

Above these critical transmissibility values, we find that the PGFs H_0^W and H_0^M no longer sum to 1. That is, above T^c , there is a probability that $\langle s_w \rangle$ won't be finite. For any sized network, the disease will occupy a proportion of that network. The probability of this happening, $S_W(T, \mu)$, is the probability that the disease won't spread to a finite number of people. That probability is

$$\sum_{s=0}^{\infty} P_s(T, \mu) = H_0^W(1; T, \mu)$$

Thus,

$$\begin{aligned} S_W(T, \mu) &= 1 - H_0^W(1; T, \mu) \\ &= 1 - G_0^W(H_1^W(1; T, \mu), 1; T, \mu). \end{aligned}$$

Then,

$$H_1^W(1; T, \mu) = G_1^W(H_1^W(1; T, \mu), 1; T, \mu)$$

Thus,

$$S_W(T, \mu) = 1 - G_0^W(u_w, 1; T, \mu)$$

where u_w is the solution to the equation

$$u_w = G_1^W(u_w, 1; T, \mu).$$

This concept also applies to the probability of a large component epidemic of the mutant virus, $S_M(T, \mu, T_\mu)$.

$$\begin{aligned} S_M(T, \mu, T_\mu) &= 1 - \sum_{s=0}^{\infty} Q(T, \mu, T_\mu u) \\ &= 1 - H_0^M(1; T, \mu, T_\mu) \end{aligned}$$

Where

$$\begin{aligned} H_0^M(1; T, \mu, T_\mu) &= G_0^W(u_m, v_m; T, \mu, T_\mu) \\ u_m &= G_1^W(u_m, v_m; T, \mu, T_\mu) \\ v_m &= G_1^M(v_m; T_\mu u) \end{aligned}$$

The numbers u_w , u_m , and v_m can all be solved for numerically. Note that u_w is the probability that the node at the end of a randomly chosen edge connected to a wild-type node remains uninfected, u_m is the probability that the node at the end of a randomly chosen edge connected to a wild-type node remains uninfected, and v_m is the probability that the node at the end of a randomly chosen edge connected to a mutant node remains uninfected.

3.2 Simulations

Using MatLab, we can code simulations on actual networks of a finite size with degree distributions that approximate Poisson, exponential, and scale-free distributions. The inputs into the simulation are T , the transmissibility value for the wild-type disease, T_μ , the transmissibility value for the mutant disease, μ , the probability that the wild-type disease will mutate to become the mutant disease and the Network, a structure consisting of an array of Nodes. Each Node in the array has two pieces of information associated with it: its degree and the array positions of its neighbors. For example, a node may have Degree 3 and Neighbors at 78, 391, and 409.

The networks used to run the simulations differ from the idealized networks of the analytical model. First, the analytical model assumes that the

network is infinite, while the real networks have a finite size. The model also assumes that the networks are completely tree-like, that is the networks have no loops. The networks used for the simulations, on the other hand, contain loops. Lastly, the degree distributions of the real networks only approximate the actual distributions.

3.2.1 Simulation Algorithm

INPUT: Wild-type transmissibility, T ; Mutant Transmissibility, T_μ ; Probability of mutation, μ .

OUTPUT: Number of wild-type infections, Num_Infected_Wildtype; number of mutant infections, Num_Infected_Mutant.

- Step 1: Set N equal to the size of the network.
- Step 2: Set Num_Infected_Wildtype = 0.
- Step 3: Set Num_Infected_Mutant = 0.
- Step 4: Create an empty array Wildtype_Infected_Vector of size 0.
- Step 5: Create an empty array Mutant_Infected_Vector of size 0.
- Step 6: Create an array of N ones, Susceptible.
- Step 7: Pick a random integer, Start_Node, between 1 and N.
- Step 8: Add Start_Node to Wildtype_Infected_Vector.
- Step 9: Num_Infected_Wildtype = 1.
- Step 10: While Wildtype_Infected_Vector is not empty or Mutant_Infected_Vector is not empty do Steps 11-36.
- Step 11: While Wildtype_Infected_Vector is not empty then do Steps 12-25.
- Step 12: Create the array Wildtype_Infected_Neighbors, consisting of all neighbors of Wildtype_Infected_Vector(1).
- Step 13: Set L equal to the Length of Wildtype_Infected_Neighbors.
- Step 14: For $i = 1$ to L do Steps 15 - 26.
- Step 15: Pick a random number between 0 and 1, r .
- Step 16: Set Neighbor equal to Wildtype_Infected_Neighbors(i).
- Step 17: If $r < (T \times \text{Susceptible}(\text{Neighbor}))$, (if T is within the transmissible range and Neighbor has not been previously infected) then do Steps 18-24.
- Step 18: Pick a random number between 0 and 1, r_μ .
- Step 19: If $r_\mu < \mu$, then do Steps 20 - 21.
- Step 20: Add Neighbor to Mutant_Infected_Vector.
- Step 21: Add 1 to Num_Infected_Mutant.
- Step 22: If $r_\mu \geq \mu$, then do Steps 22 - 23.

Step 23: Add Neighbor to Wildtype_Infected_Vector.
 Step 24: Add 1 to Num_Infected_Wildtype.
 Step 25: Set Susceptible(Neighbor) equal to 0.
 Step 26: Remove the first element from Wildtype_Infected_Vector
 Step 27: While Mutant_Infected_Vector is not empty then do Steps 27 -
 36.
 Step 28: Create the array Mutant_Infected_Neighbors, consisting of
 all neighbors of Mutant_Infected_Vector(1).
 Step 29: Set L equal to the length of the array Mutant_Infected_Neighbors.
 Step 30: For i = 1 to L do steps 30 - 34
 Step 31: Pick a random number between 0 and 1, r.
 Step 32: Set Neighbor equal to Mutant_Infected_Neighbors(i).
 Step 33: If $r < (T_\mu \times \text{Susceptible}(\text{Neighbor}))$ then do Steps 33-34.
 Step 34: Add Neighbor to Mutant_Infected_Vector.
 Step 35: Add 1 to Num_Infected_Mutant.
 Step 36: Remove the first element from Wildtype_Infected_Vector.
 Step 37: OUTPUT Num_Infected_Wildtype and Num_Infected_Mutant. STOP.

This simulation can then be run several times for each network for a range
 of T values between 0 and 1 to get an average size for each T value. It can
 also be run over the range of T_μ values and μ values. [See Appendix B for
 MatLab code]

Chapter 4

Results

4.1 Predicted Values for a Mutating Pathogen

It is important to look at the behavior of $\langle s_w \rangle$, $\langle s_m \rangle$, $S_w(T, \mu)$, and $S_m(T_\mu)$ as T , T_μ and μ vary. Figure 2 shows $\langle s_w \rangle$ for a Poisson network (red), an exponential network (green) and a Scale-Free network (blue) for T values between 0 and .25 with $T_\mu = .3$ and $\mu = .1$. The three graphs (Figures 4.1, 4.2, and 4.3) show this behavior. There is not a graph for $\langle s_m \rangle$ because $T_\mu > T_\mu^c$.

4.2 Simulation

Using the data obtained from a large number of simulations ($N = 1000$) over a range of T values, we can observe how both the size and probability of an epidemic vary with T . Figures 4.4, 4.5, and 4.6 show how the simulated proportion of infected individuals in an epidemic varies as a function the transmissibility T . For each network type they show the average number of people infected with each type of infection, given that the number of people infected is greater than 75 and that the other parameters are fixed at $T_\mu = .3$ and $\mu = .1$. Figures 4.7-4.9 show the same thing when $T_\mu = .1$ and $\mu = .1$.

The simulations can also be used to calculate the probability of an epidemic. To do this, 1000 simulations were run and the number of infected individuals for each simulation was sorted into a histogram with 100 bins. The number of simulations in the upper two-thirds of the bins were counted as epidemics and that number divided by the total number of simulations gives the probability. This cutoff works for the parameters used to generate figures 4.10-4.15 but it is not the best way to sort the data because it will count non-epidemics at lower transmissibility values and it will not count

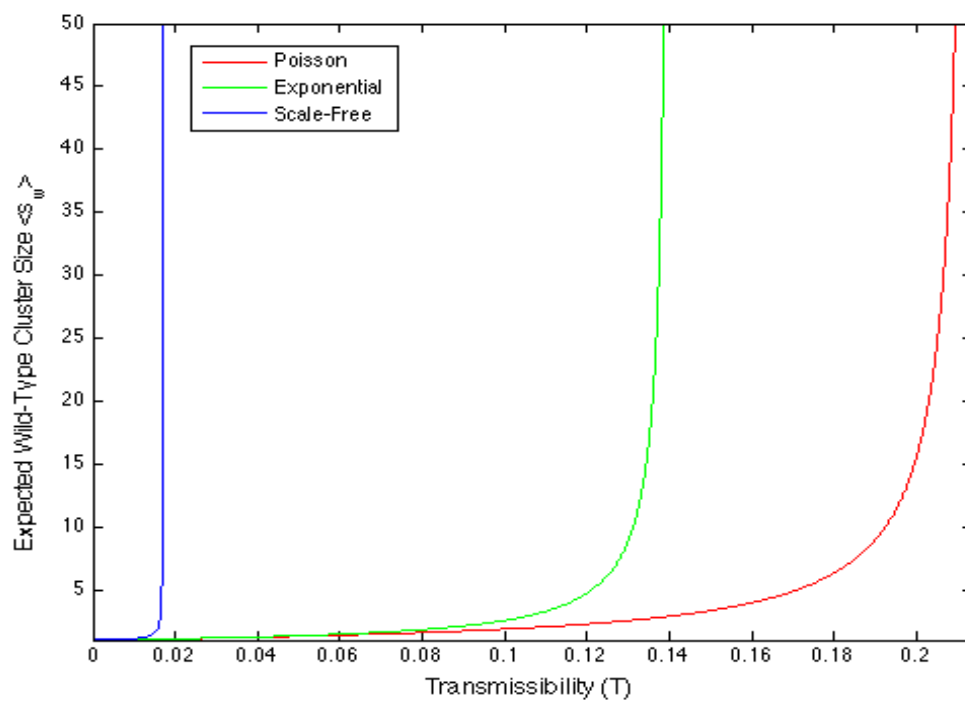


Figure 4.1: $\langle s_w \rangle$ as a function of T for Poisson, Exponential and Scale-free Networks ($T_\mu = .3$, $\mu = .1$). This graph resembles the graph of $\langle s \rangle$ for the basic model (Figure 2).

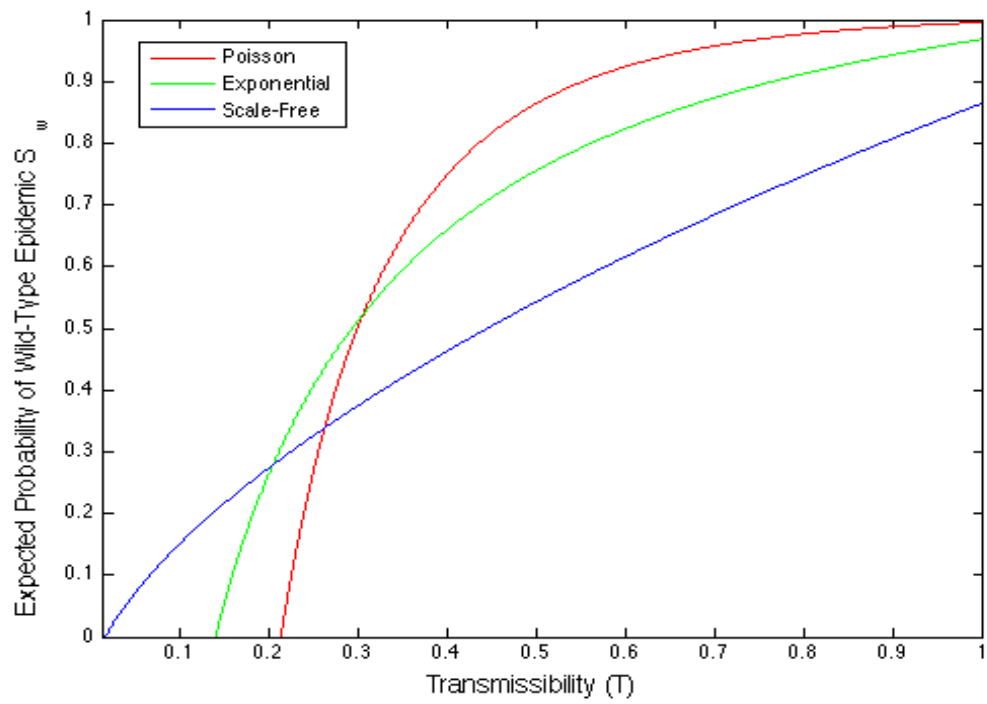


Figure 4.2: $S_w(T, \mu, T_\mu)$ as a function of T for Poisson, Exponential and Scale-free Networks ($T_\mu = .3$, $\mu = .1$)

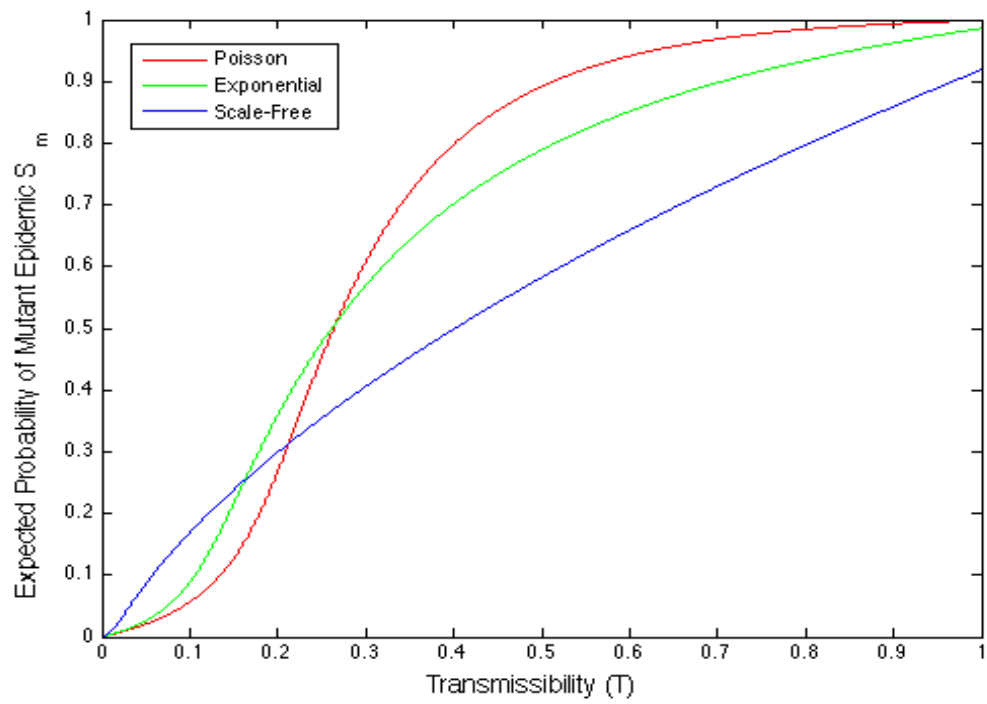


Figure 4.3: $S_m(T, \mu, T_\mu)$ as a function of T for Poisson, Exponential and Scale-free Networks ($T_\mu = .3$, $\mu = .1$)

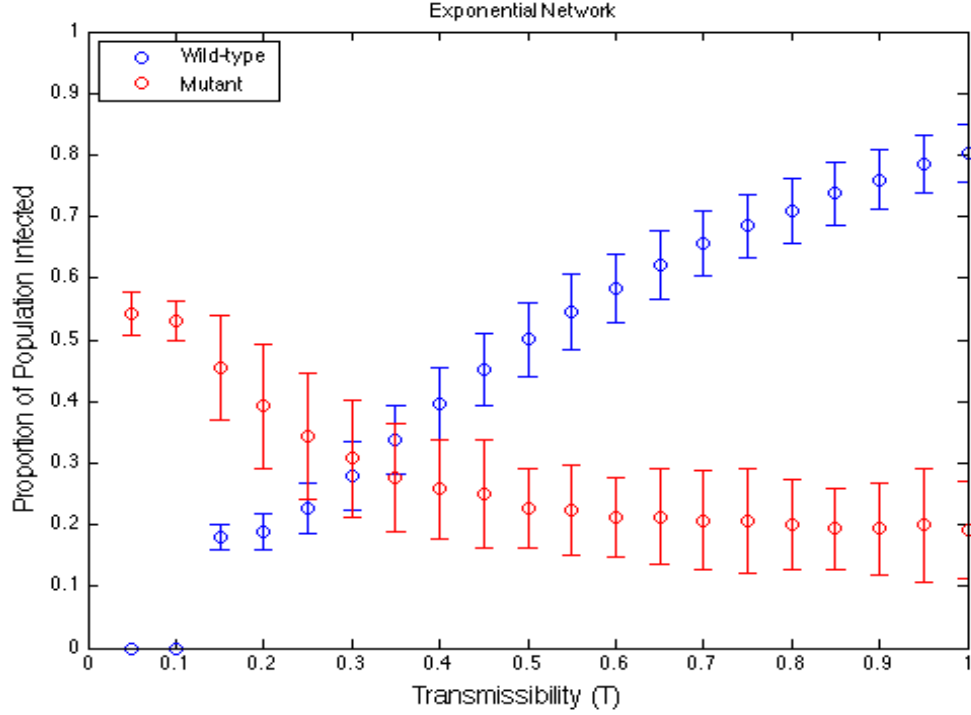


Figure 4.4: Wild-type (blue) and mutant (red) infections as a function of T for an Exponential network with 500 nodes, mean degree 5, and parameters $T_\mu = .3$, $\mu = .1$. The error bars show the standard deviation of the value.

small epidemics at high transmissibility values. We can see from figures 4.10-4.12 that S_w accurately predicts the probability of a wild-type epidemic for all three networks. On the other hand, figures 4.13-4.15 show that S_m does not always accurately predict the probability of a mutant outbreak under these conditions.

4.3 Naive-Treated Dynamics

The first step towards the full model of a mutating pathogen spreading over a two-type network is to model the dynamics of disease spread over that network. In this case, the two types of nodes in the network are *naive* nodes, representing untreated individuals in a population, and *immunized* nodes, representing individuals in a population who have had some sort of treatment, for example an immunization or prophylactic drug like TamiFlu. In theory, these two should have different probabilities of catching a disease

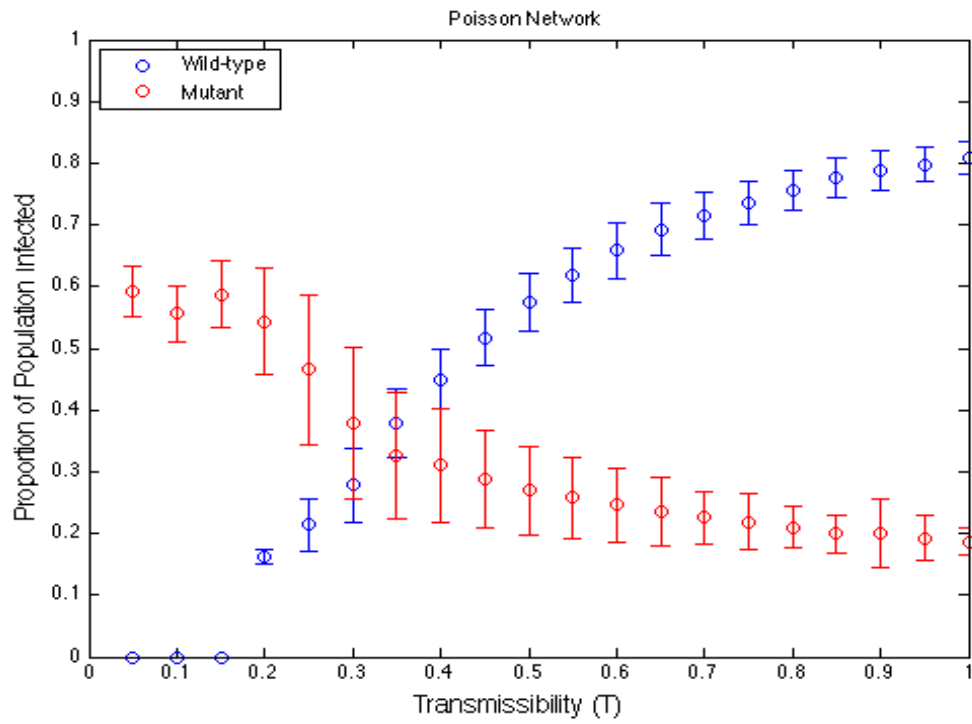


Figure 4.5: Wild-type (blue) and mutant (red) infections as a function of T for a Poisson network with 500 nodes, mean degree 5, and parameters $T_\mu = .3$, $\mu = .1$. The error bars show the standard deviation of the value.

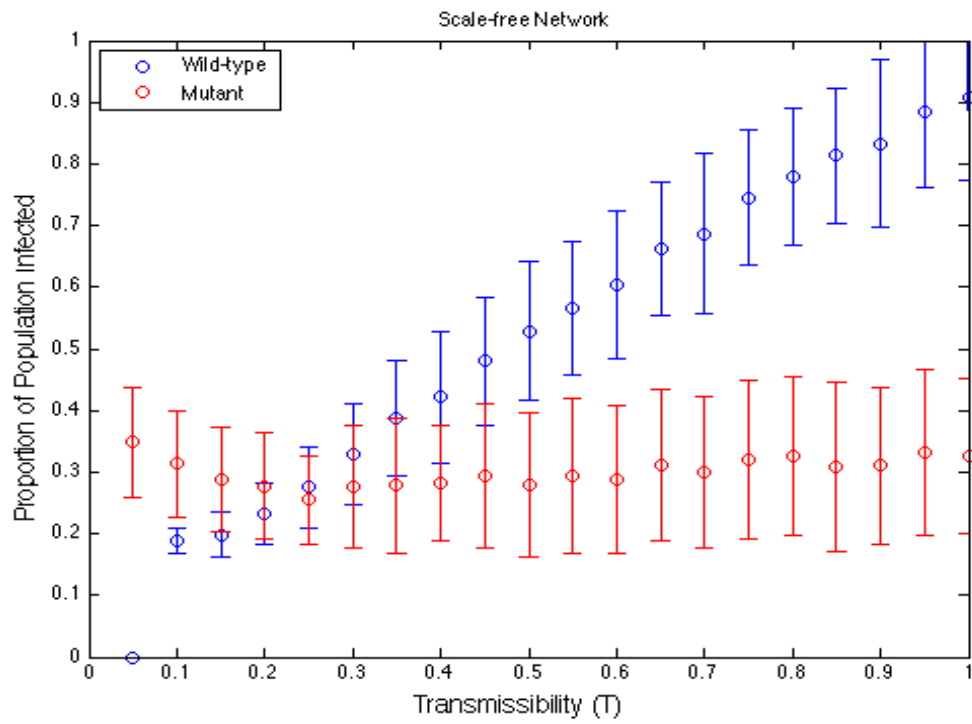


Figure 4.6: Wild-type (blue) and mutant (red) infections as a function of T for a Scale-free network with 500 nodes, mean degree 5, and parameters $T_\mu = .3$, $\mu = .1$. The error bars show the standard deviation of the value.

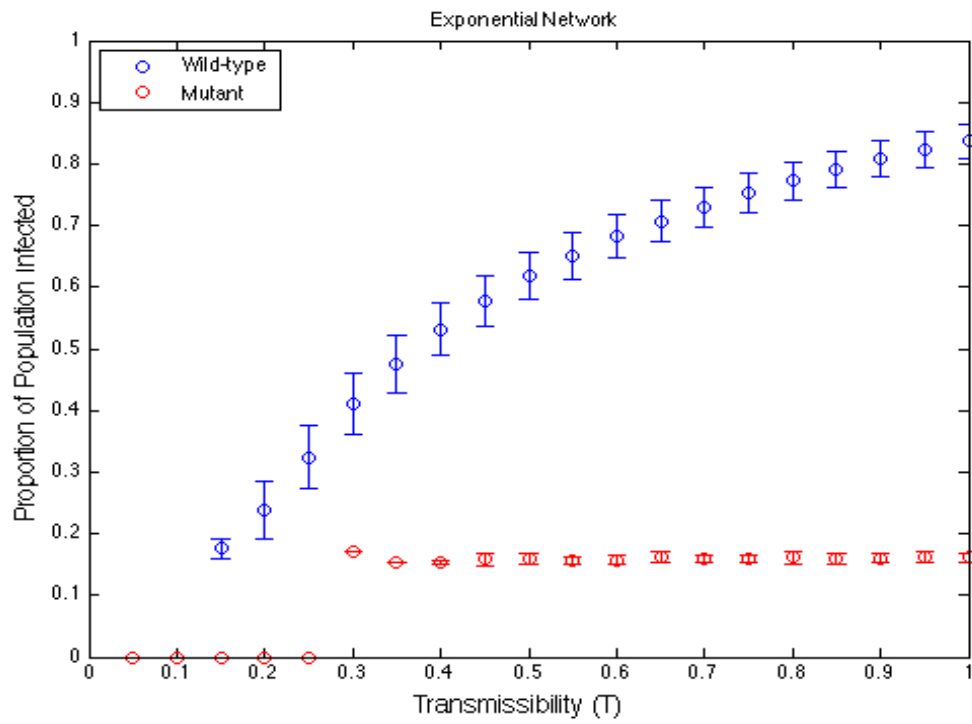


Figure 4.7: Wild-type (blue) and mutant (red) infections as a function of T for an Exponential network with 500 nodes, mean degree 5, and parameters $T_\mu = .1$, $\mu = .1$. The error bars show the standard deviation of the value.

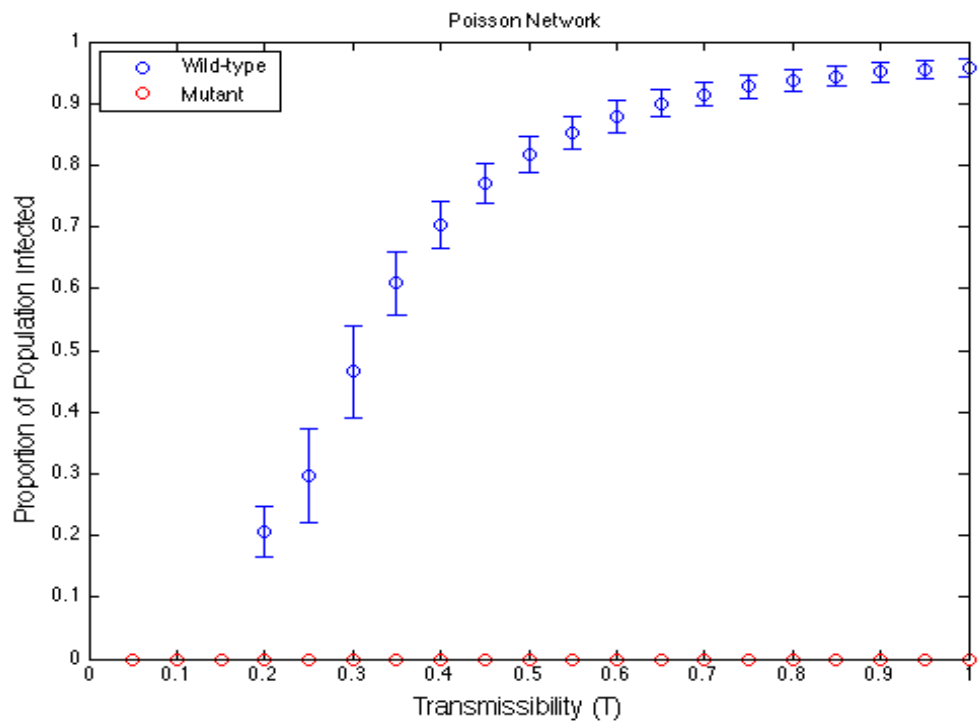


Figure 4.8: Wild-type (blue) and mutant (red) infections as a function of T for a Poisson network with 500 nodes, mean degree 5, and parameters $T_\mu = .1$, $\mu = .1$. The error bars show the standard deviation of the value.

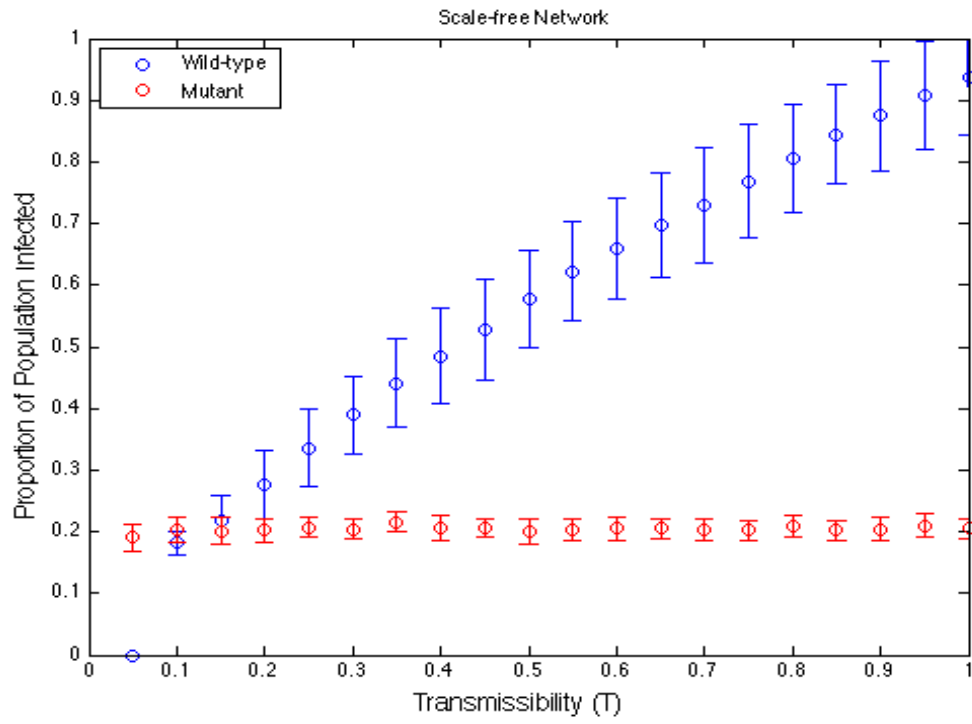


Figure 4.9: Wild-type (blue) and mutant (red) infections as a function of T for a Scale-free network with 500 nodes, mean degree 5, and parameters $T_\mu = .1$, $\mu = .1$. The error bars show the standard deviation of the value.

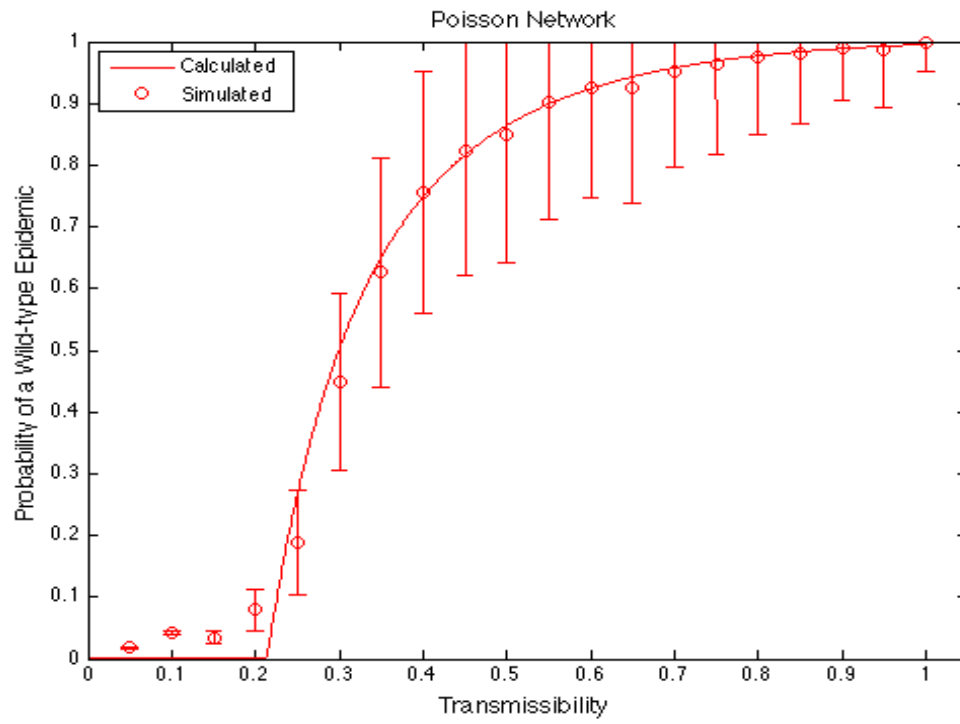


Figure 4.10: Calculated and Simulated values of S_w for a Poisson network with 500 nodes, mean degree 5 and parameters $T_\mu = .3$ and $\mu = .1$.

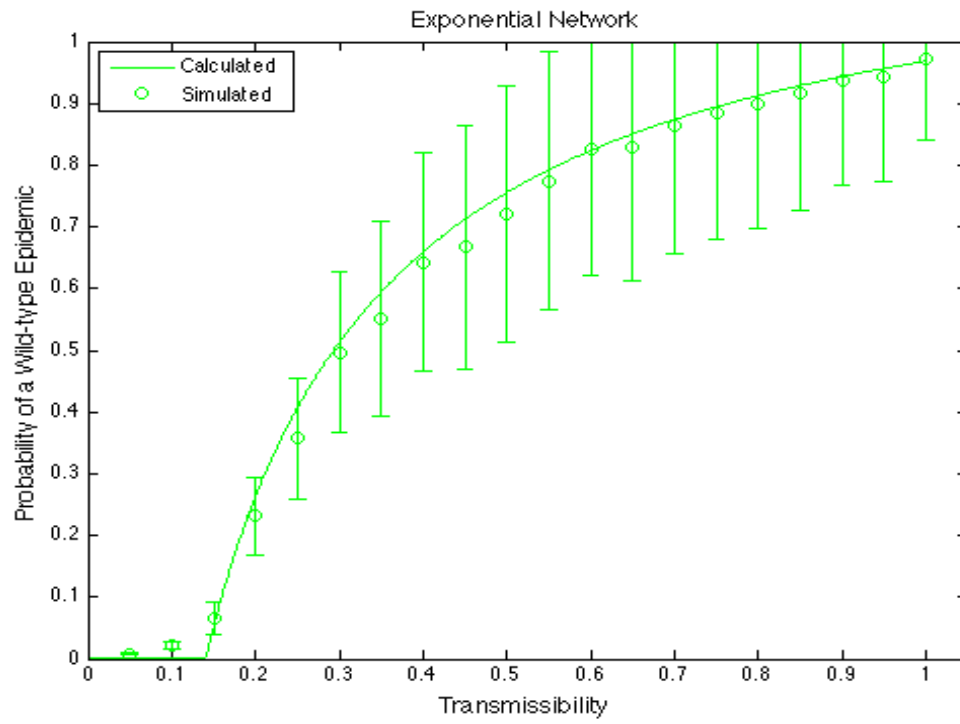


Figure 4.11: Calculated and Simulated values of S_w for an Exponential network with 500 nodes, mean degree 5 and parameters $T_\mu = .3$ and $\mu = .1$.

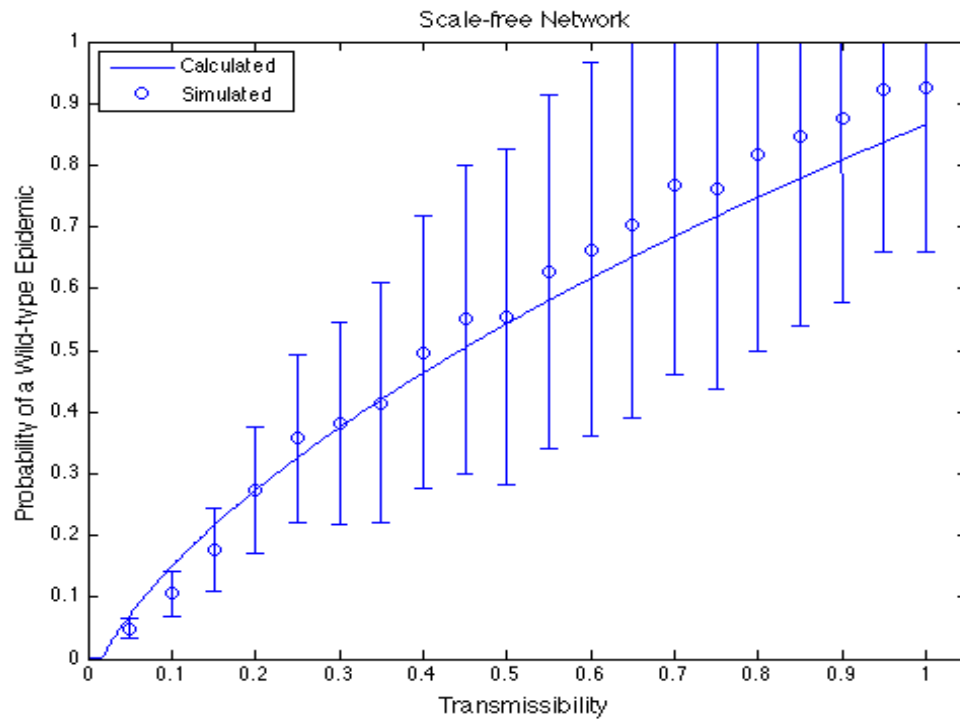


Figure 4.12: Calculated and Simulated values of S_w for a Scale-free network with 500 nodes, mean degree 5 and parameters $T_\mu = .3$ and $\mu = .1$.

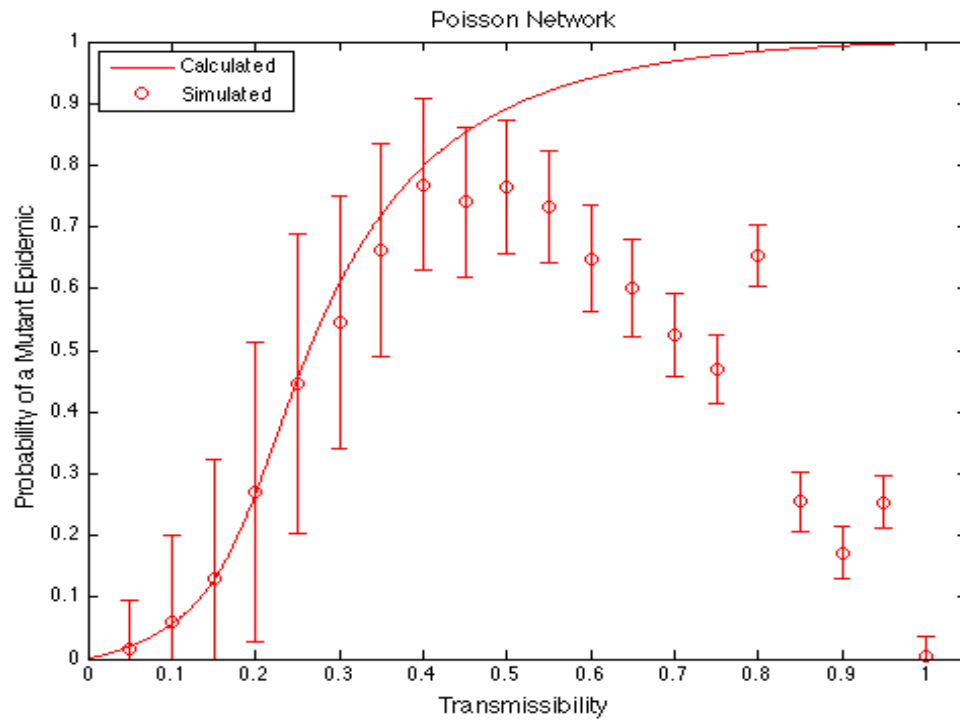


Figure 4.13: Calculated and Simulated values of S_m for a Poisson network with 500 nodes, mean degree 5 and parameters $T_\mu = .3$ and $\mu = .1$.

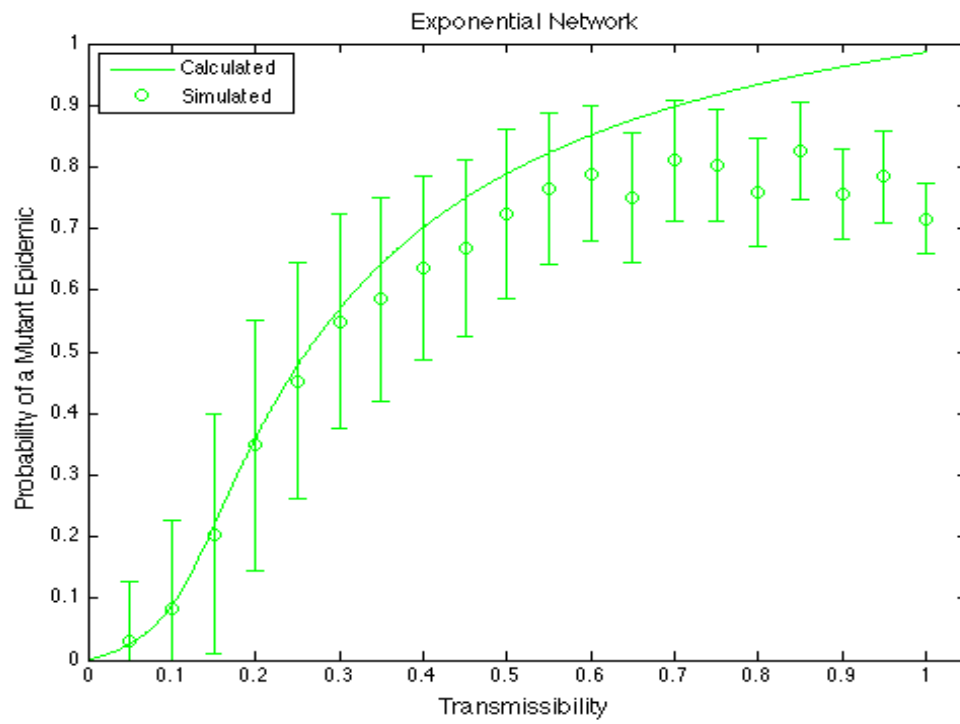


Figure 4.14: Calculated and Simulated values of S_m for an Exponential network with 500 nodes, mean degree 5 and parameters $T_\mu = .3$ and $\mu = .1$. The error bars show the standard deviation of the value.

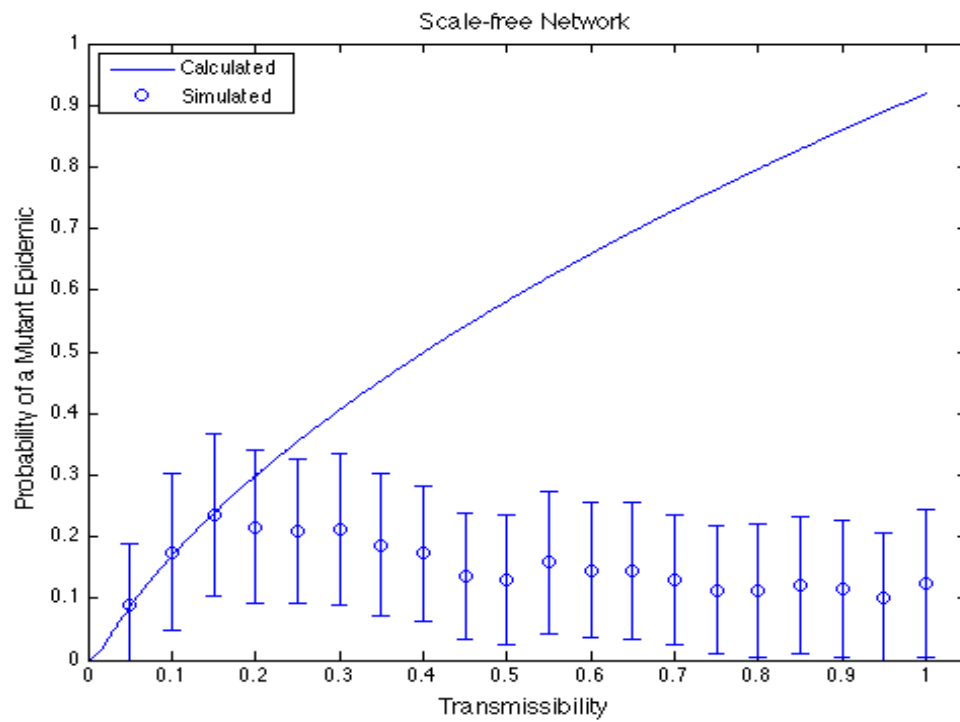


Figure 4.15: Calculated and Simulated values of S_m for a Scale-free network with 500 nodes, mean degree 5 and parameters $T_\mu = .3$ and $\mu = .1$. The error bars show the standard deviation of the value.

and of spreading the disease.

4.3.1 Generating Functions

The generating functions describing this model are different from previous models because we must now account for two types of nodes. First, there are two degree distributions:

$$F_0(x, y) = \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} p_{jk} x^j y^k$$

is the PGF for the degree distribution for naive nodes where p_{jk} represents the proportion of naive nodes that have j naive neighbors and k immunized neighbors. The average number of naive contacts a naive individual has, $\langle j \rangle$, can be found by:

$$\langle j \rangle = \left. \frac{\partial F_0(x, y)}{\partial x} \right|_{x=1, y=1} = \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} j p_{jk} = \sum_{j=0}^{\infty} j p_j$$

Similarly, the average number of immunized nodes connected to a naive node, $\langle k \rangle$ can be found by:

$$\langle k \rangle = \left. \frac{\partial F_0(x, y)}{\partial y} \right|_{x=1, y=1} = \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} k p_{jk} = \sum_{k=0}^{\infty} k p_k$$

Similarly,

$$G_0(x, y) = \sum_{l=0}^{\infty} \sum_{m=0}^{\infty} q_{lm} x^l y^m$$

is the PGF for the degree distribution for immunized nodes and the mean naive degree and immunized degree, $\langle l \rangle$ and $\langle m \rangle$, respectively, are:

$$\langle l \rangle = \left. \frac{\partial G_0(x, y)}{\partial x} \right|_{x=1, y=1} = \sum_{l=0}^{\infty} \sum_{m=0}^{\infty} l p_{lm} = \sum_{l=0}^{\infty} l p_l$$

and

$$\langle m \rangle = \left. \frac{\partial G_0(x, y)}{\partial y} \right|_{x=1, y=1} = \sum_{l=0}^{\infty} \sum_{m=0}^{\infty} m p_{lm} = \sum_{m=0}^{\infty} m p_m$$

The next step is to consider the excess degree distributions of each type of node. A naive node can be connected to both naive nodes and immunized so it will have two excess degree distributions: $F_1^N(x, y)$, the PGF for the

number of excess naive edges and the number of immunized edges for a naive node found by following a random naive-naive edges to its end and $F_1^I(x, y)$, the PGF for the number of naive edges and the number of excess immunized edges for a naive node found by following a random immunized-naive edges to its end. They are given by

$$F_1^N(x, y) = \frac{1}{\langle j \rangle} \frac{\partial F_0}{\partial x}$$

and

$$F_1^I(x, y) = \frac{1}{\langle k \rangle} \frac{\partial F_0}{\partial y}$$

An immunized may also be reached from either type of node, so it has two excess degree distributions as well. The excess naive degree distribution for a immunized node is given by

$$G_1^N(x, y) = \frac{1}{\langle l \rangle} \frac{\partial G_0}{\partial x}$$

The excess immunized degree distribution for a immunized node is given by

$$G_1^I(x, y) = \frac{1}{\langle m \rangle} \frac{\partial G_0}{\partial y}$$

4.3.2 Disease Transmission

Depending on the treatment, the transmissibility value will vary for each type of edge. If an individual is prophylactically treated to protect against a certain disease, her probability contracting that pathogen may be greatly reduced or even eliminated entirely. Furthermore, a treated individual may have a shorter or less severe case of a disease, decreasing his or her chance of spreading it. Therefore, this model uses four separate transmissibility values: T_{NN} for transmission between naive individuals, T_{NI} for transmission from a naive individual to a treated individual, T_{IN} for transmission from a treated individual to a naive individual, and T_{II} for transmission between two infected individuals. For a naive individual with j naive edges and k treated edges, the probability of transmitting the disease to exactly m of the naive edges and n of the treated edges is:

$$\binom{j}{m} (T_{NN})^m (1 - T_{NN})^{j-m} \binom{k}{n} (T_{NI})^n (1 - T_{NI})^{k-n}$$

So, the occupied degree distribution for a naive individual is:

$$F_0(x, y; T_{NN}, T_{NI}) =$$

$$\begin{aligned}
& \sum_{m=0}^{\infty} \sum_{n=0}^{\infty} \sum_{j=m}^{\infty} \sum_{k=n}^{\infty} \binom{j}{m} (T_{NN})^m (1 - T_{NN})^{j-m} \binom{k}{n} (T_{NI})^n (1 - T_{NI})^{n-k} p_{jk} x^m y^n \\
&= \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} p_{jk} \sum_{m=0}^j \sum_{n=0}^k \binom{j}{m} (T_{NN})^m (1 - T_{NN})^{j-m} \binom{k}{n} (T_{NI})^n (1 - T_{NI})^{n-k} x^m y^n \\
&= \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} p_{jk} \sum_{m=0}^j (x T_{NN})^m (1 - T_{NN})^{j-m} \sum_{n=0}^k \binom{k}{n} (y T_{NI})^n (1 - T_{NI})^{n-k} \\
&= \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} p_{jk} [(1 - T_{NN} + T_{NN}x)^j (1 - T_{NI} + T_{NI}y)^k] \\
&= F_0(1 + (x - 1)T_{NN}, 1 + (y - 1)T_{NI})
\end{aligned}$$

Similarly, for the excess degree distributions F_1^N and F_1^I are given by:

$$F_1^N(x, y; T_{NN}, T_{NI}) = F_1^N(1 + (x - 1)T_{NN}, 1 + (y - 1)T_{NI}),$$

and

$$F_1^I(x, y; T_{NN}, T_{NI}) = F_1^I(1 + (x - 1)T_{NN}, 1 + (y - 1)T_{NI})$$

Furthermore, the same derivations can be done for G_0 , G_1^N and G_1^I :

$$G_0(x, y; T_{IN}, T_{II}) = G_0(1 + (x - 1)T_{IN}, 1 + (y - 1)T_{II}),$$

$$G_1^N(x, y; T_{IN}, T_{II}) = G_1^N(1 + (x - 1)T_{IN}, 1 + (y - 1)T_{II}),$$

and

$$G_1^I(x, y; T_{IN}, T_{II}) = G_1^I(1 + (x - 1)T_{IN}, 1 + (y - 1)T_{II})$$

4.3.3 Properties

These generating functions have important properties that we will use later. First, they are all normalized, so we have:

$$\begin{aligned}
F_0(1, 1; T_{NN}, T_{NI}) &= F_0(1 + (1 - 1)T_{NN}, 1 + (1 - 1)T_{NI}) \\
&= F_0(1, 1) = 1.
\end{aligned}$$

Similarly,

$$\begin{aligned}
F_1^N(1, 1; T_{NN}, T_{NI}) &= F_1^N(1, 1) = 1 \\
F_1^I(1, 1; T_{NN}, T_{NI}) &= F_1^I(1, 1) = 1, \\
G_0(1, 1; T_{IN}, T_{II}) &= G_0(1, 1) = 1, \\
G_1^N(1, 1; T_{IN}, T_{II}) &= G_1^N(1, 1) = 1,
\end{aligned}$$

and

$$G_1^I(1, 1; T_{IN}, T_{II}) = G_1^I(1, 1) = 1.$$

We also see that when the transmissibility values are 1, all edges will be occupied:

$$\begin{aligned} F_0(x, y; 1, 1) &= F_0(1 + x - 1, 1 + y - 1) \\ &= F_0(x, y). \end{aligned}$$

Similarly,

$$\begin{aligned} F_1^N(x, y; 1, 1) &= F_1^N(x, y), \\ F_1^I(x, y; 1, 1) &= F_1^I(x, y), \\ G_0(x, y; 1, 1) &= G_0(x, y), \\ G_1^N(x, y; 1, 1) &= G_1^N(x, y), \end{aligned}$$

and

$$G_1^I(x, y; 1, 1) = G_1^I(x, y).$$

Furthermore, we can see that the expected number of occupied edges connected to a node is expected number of nodes connected to that times the probability of that type of edge being occupied.

$$\left. \frac{\partial F_0(x, y; T_{NN}, T_{NI})}{\partial x} \right|_{x=1, y=1} = T_{NN} \left. \frac{\partial F_0(x, y)}{\partial x} \right|_{x=1, y=1} = T_{NN} < j >$$

$$\left. \frac{\partial F_0(x, y; T_{NN}, T_{NI})}{\partial y} \right|_{x=1, y=1} = T_{NI} \left. \frac{\partial F_0(x, y)}{\partial y} \right|_{x=1, y=1} = T_{NI} < k >$$

$$\left. \frac{\partial G_0(x, y; T_{IN}, T_{II})}{\partial x} \right|_{x=1, y=1} = T_{IN} \left. \frac{\partial G_0(x, y)}{\partial x} \right|_{x=1, y=1} = T_{IN} < l >$$

$$\left. \frac{\partial G_0(x, y; T_{IN}, T_{II})}{\partial y} \right|_{x=1, y=1} = T_{II} \left. \frac{\partial G_0(x, y)}{\partial y} \right|_{x=1, y=1} = T_{II} < m >$$

Lastly, the expected number of excess occupied edges connected a node is just the probability of transmission along that type of edge times the average number of excess edges.

$$\left. \frac{\partial F_1^N(x, y; T_{NN}, T_{NI})}{\partial x} \right|_{x=1, y=1} = T_{NN} \left. \frac{\partial F_1^N(x, y)}{\partial x} \right|_{x=1, y=1} = T_{NN} < j_e >$$

$$\left. \frac{\partial F_1^N(x, y; T_{NN}, T_{NI})}{\partial y} \right|_{x=1, y=1} = T_{NI} \left. \frac{\partial F_1^N(x, y)}{\partial y} \right|_{x=1, y=1} = T_{NI} \frac{\langle jk \rangle}{\langle j \rangle}$$

$$\left. \frac{\partial F_1^I(x, y; T_{NN}, T_{NI})}{\partial x} \right|_{x=1, y=1} = T_{NN} \left. \frac{\partial F_1^N(x, y)}{\partial x} \right|_{x=1, y=1} = T_{NN} \frac{\langle jk \rangle}{\langle k \rangle}$$

$$\left. \frac{\partial F_1^I(x, y; T_{NN}, T_{NI})}{\partial y} \right|_{x=1, y=1} = T_{NI} \left. \frac{\partial F_1^N(x, y)}{\partial y} \right|_{x=1, y=1} = T_{NI} \langle k_e \rangle$$

$$\left. \frac{\partial G_1^N(x, y; T_{IN}, T_{II})}{\partial x} \right|_{x=1, y=1} = T_{IN} \left. \frac{\partial G_1^I(x, y)}{\partial x} \right|_{x=1, y=1} = T_{IN} \langle l_e \rangle$$

$$\left. \frac{\partial G_1^N(x, y; T_{IN}, T_{II})}{\partial y} \right|_{x=1, y=1} = T_{II} \left. \frac{\partial G_1^I(x, y)}{\partial y} \right|_{x=1, y=1} = T_{II} \frac{\langle lm \rangle}{\langle l \rangle}$$

$$\left. \frac{\partial G_1^I(x, y; T_{IN}, T_{II})}{\partial x} \right|_{x=1, y=1} = T_{IN} \left. \frac{\partial G_1^I(x, y)}{\partial x} \right|_{x=1, y=1} = T_{IN} \frac{\langle lm \rangle}{\langle m \rangle}$$

$$\left. \frac{\partial G_1^I(x, y; T_{IN}, T_{II})}{\partial y} \right|_{x=1, y=1} = T_{II} \left. \frac{\partial G_1^I(x, y)}{\partial y} \right|_{x=1, y=1} = T_{II} \langle m_e \rangle$$

where

$$\langle j_e \rangle = \left. \frac{\partial F_1^N(x, y; \mathbf{T})}{\partial x} \right|_{x=1, y=1} = \frac{\langle j^2 \rangle - \langle j \rangle}{\langle j \rangle}$$

is the average excess naive degree of a naive node. And similarly for $\langle k_e \rangle$, $\langle l_e \rangle$, and $\langle m_e \rangle$. Furthermore,

$$\langle jk \rangle = \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} jk p_{jk}$$

and similarly for $\langle lm \rangle$.

4.4 Finding the Size of the Epidemic

To find the size of an epidemic, we find the size of a cluster of infected nodes attached to a node. Because there are two types of node, naive and treated, we naturally have two generating functions,

$$H_0^N(x, y; \mathbf{T}) = \sum_{s,t} P_{s,t}(\mathbf{T}) x^s y^t$$

and

$$H_0^I(x, y; \mathbf{T}) = \sum_{s,t} Q_{s,t}(\mathbf{T}) x^s y^t,$$

where x counts the number of naive individuals infected, y counts the number of treated individuals infected, and \mathbf{T} is the vector of transmissibility values $\{T_{NN}, T_{NI}, T_{IN}, T_{II}\}$.

To find H_0^N and H_0^I , consider the generating functions of the size of a cluster of attached to a randomly chosen edge. There are four types of edges (naive-naive, naive-treated, naive-immunized, and immunized-immunized) thus there are four such generating functions. If you pick a random edge between two naive nodes and follow it to a node, the generating function will be x , counting that node, multiplied by its excess naive occupied degree $F_0^N(x, y; \mathbf{T})$. However, each of those edges can generate a cluster, so the arguments of F_0^N will be H_1^{NN} the generating function for cluster sizes connected to a naive-to-naive edge and H_1^{NI} the generating function for cluster sizes connected to a naive-to-immunized edge. Thus, the PGF for the size of the disease cluster found by following a Naive-Naive edge is:

$$H_1^{NN}(x, y; \mathbf{T}) = x F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}).$$

Likewise, for the other types of edges, we have:

$$H_1^{NI}(x, y; \mathbf{T}) = y G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}),$$

$$H_1^{IN}(x, y; \mathbf{T}) = x F_1^I(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}),$$

and

$$H_1^{II}(x, y; \mathbf{T}) = y G_1^I(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}).$$

Then the PGF for the size of a cluster attached to a random naive node will be x times the occupied degree distribution of a naive node whose arguments are the generating functions for the size of clusters attached to naive-naive and naive-immunized edges, respectively:

$$H_0^N(x, y; \mathbf{T}) = xF_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}).$$

Similarly, the PGF for the size of a cluster attached to a random naive node is:

$$H_0^I(x, y; \mathbf{T}) = yG_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})$$

To find the size of an epidemic, we find the expected value of the cluster size attached to a node. To do this, we take the appropriate partial derivative with respect to the appropriate PGf. The expected number of naive individuals in an outbreak emanating from a naive node is

$$\begin{aligned} \langle s_{NN} \rangle &= \left. \frac{\partial H_0^N}{\partial x} \right|_{x=1, y=1} \\ &= 1 + \left[T_{NN} \langle j \rangle \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} + T_{NI} \langle k \rangle \left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1} \right]. \end{aligned}$$

Similarly, the expected number of immunized individuals in an outbreak emanating from a naive node is

$$\begin{aligned} \langle s_{NI} \rangle &= \left. \frac{\partial H_0^N}{\partial y} \right|_{x=1, y=1} \\ &= \left[T_{NN} \langle j \rangle \left. \frac{\partial H_1^{NN}}{\partial y} \right|_{x=1, y=1} + T_{NI} \langle k \rangle \left. \frac{\partial H_1^{NI}}{\partial y} \right|_{x=1, y=1} \right], \end{aligned}$$

The average number of naive individuals in a cluster extending from an immunized node is

$$\begin{aligned} \langle s_{IN} \rangle &= \left. \frac{\partial H_0^I}{\partial x} \right|_{x=1, y=1} \\ &= \left[T_{IN} \langle l \rangle \left. \frac{\partial H_1^{IN}}{\partial x} \right|_{x=1, y=1} + T_{II} \langle m \rangle \left. \frac{\partial H_1^{II}}{\partial x} \right|_{x=1, y=1} \right]. \end{aligned}$$

Lastly, the expected number of immunized individuals in an outbreak emanating from an immunized node is

$$\begin{aligned} \langle s_{II} \rangle &= \left. \frac{\partial H_0^I}{\partial y} \right|_{x=1, y=1} \\ &= 1 + \left[T_{IN} \langle l \rangle \left. \frac{\partial H_1^{IN}}{\partial y} \right|_{x=1, y=1} + T_{II} \langle m \rangle \left. \frac{\partial H_1^{II}}{\partial y} \right|_{x=1, y=1} \right]. \end{aligned}$$

(For full derivations, see Appendix C)

In order to fully understand these results, we must calculate the partial derivatives of H_1^{NN} , H_1^{NI} , H_1^{IN} , and H_1^{II} . In doing so, we get a two systems of equations for the partial derivatives evaluated at $x = 1, y = 1$. Solving these equations give us:

$$\begin{aligned}\left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} &= \frac{1 - T_{II} \langle m_e \rangle}{\Delta} \\ \left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1} &= \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})][T_{II}T_{IN}\frac{\langle lm \rangle^2}{\langle l \rangle \langle m \rangle} + T_{IN} \langle l_e \rangle (1 - T_{II} \langle m_e \rangle)]}{\Delta} \\ \left. \frac{\partial H_1^{IN}}{\partial x} \right|_{x=1, y=1} &= \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})](1 - T_{II} \langle m_e \rangle)}{\Delta} \\ \left. \frac{\partial H_1^{II}}{\partial x} \right|_{x=1, y=1} &= \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})](T_{IN} \frac{\langle lm \rangle}{\langle m \rangle})}{\Delta}\end{aligned}$$

for the partial derivatives with respect to x, and

$$\begin{aligned}\left. \frac{\partial H_1^{NN}}{\partial y} \right|_{x=1, y=1} &= \frac{T_{NI} \frac{\langle jk \rangle}{\langle j \rangle} [1 - T_{II}(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta} \\ \left. \frac{\partial H_1^{NI}}{\partial y} \right|_{x=1, y=1} &= \frac{(1 - T_{NN} \langle j_e \rangle)[1 - T_{II}(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta} \\ \left. \frac{\partial H_1^{IN}}{\partial y} \right|_{x=1, y=1} &= \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})]T_{NI} \frac{\langle jk \rangle}{\langle j \rangle} [1 - T_{II}(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta} \\ \left. \frac{\partial H_1^{II}}{\partial y} \right|_{x=1, y=1} &= \frac{(1 - T_{NN} \langle j_e \rangle) - T_{NI} \frac{\langle jk \rangle}{\langle j \rangle} \left[T_{IN}(\langle l_e \rangle + \frac{\langle lm \rangle}{\langle m \rangle})(1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})) \right]}{\Delta}\end{aligned}$$

for the partial derivatives with respect to y.

Where

$$\Delta = \alpha\beta + \gamma$$

with

$$\begin{aligned}\alpha &= \left[1 - T_{NN} \left(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle} \right) \right] \left(-T_{NI}T_{IN} \frac{\langle jk \rangle}{\langle j \rangle} \right) \\ \beta &= \left[T_{II} \frac{\langle lm \rangle^2}{\langle l \rangle \langle m \rangle} - \langle l_e \rangle (1 - T_{II} \langle m_e \rangle) \right]\end{aligned}$$

and

$$\gamma = (1 - T_{NN} \langle j_e \rangle)(1 - T_{II} \langle m_e \rangle)$$

Thus,

$$\begin{aligned}
\langle s_{NN} \rangle &= 1 + T_{NN} \langle j \rangle \frac{1 - T_{II} \langle m_e \rangle}{\Delta} \\
&\quad + T_{NI} \langle k \rangle \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})][T_{II} T_{IN} \frac{\langle lm \rangle^2}{\langle l \rangle \langle m \rangle}]}{\Delta} \\
&\quad + T_{NI} \langle k \rangle \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})][-T_{IN} \langle l_e \rangle (1 - T_{II} \langle m_e \rangle)]}{\Delta} \\
\langle s_{NI} \rangle &= T_{NN} \langle j \rangle \frac{T_{NI} \frac{\langle jk \rangle}{\langle j \rangle} [1 - T_{II}(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta} \\
&\quad + T_{NI} \langle k \rangle \frac{(1 - T_{NN} \langle j_e \rangle)[1 - T_{II}(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta} \\
\langle s_{IN} \rangle &= T_{IN} \langle l \rangle \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})](1 - T_{II} \langle m_e \rangle)}{-\Delta} \\
&\quad + T_{II} \langle m \rangle \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})](-T_{IN} \frac{\langle lm \rangle}{\langle m \rangle})}{\Delta} \\
\langle s_{II} \rangle &= 1 + T_{IN} \langle l \rangle \frac{[1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})]T_{NI} \frac{\langle jk \rangle}{\langle j \rangle} [1 - T_{II}(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta} \\
&\quad + T_{II} \langle m \rangle \frac{(1 - T_{NN} \langle j_e \rangle)}{\Delta} \\
&\quad + T_{II} \langle m \rangle \frac{T_{NI} \frac{\langle jk \rangle}{\langle j \rangle} \left[-T_{IN}(\langle l_e \rangle + \frac{\langle lm \rangle}{\langle m \rangle})(1 - T_{NN}(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})) \right]}{\Delta}
\end{aligned}$$

To make these equations more approachable, we make the simplifying assumption that the probability of an infected individual infects an uninfected individual depends only on whether or not the uninfected individual has been treated. That is, $T_{IN} = T_{NN} = T_N$ and $T_{NI} = T_{II} = T_I$.

Then, we have

$$\Delta = \alpha' \beta' + \gamma'$$

with

$$\begin{aligned}
\alpha' &= \left[1 - T_N \left(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle} \right) \right] \left(-T_I T_N \frac{\langle jk \rangle}{\langle j \rangle} \right) \\
\beta' &= \left[T_I \frac{\langle lm \rangle^2}{\langle l \rangle \langle m \rangle} - \langle l_e \rangle (1 - T_I \langle m_e \rangle) \right]
\end{aligned}$$

and

$$\gamma' = (1 - T_N \langle j_e \rangle)(1 - T_I \langle m_e \rangle)$$

The expected values become

$$\begin{aligned} \langle s_{NN} \rangle &= 1 + T_N \langle j \rangle \frac{1 - T_I \langle m_e \rangle}{\Delta'} \\ &+ T_I \langle k \rangle \frac{[1 - T_N(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})][T_I T_N \frac{\langle lm \rangle^2}{\langle l \rangle \langle m \rangle}]}{\Delta'} \\ &+ T_I \langle k \rangle \frac{[1 - T_N(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})][-T_N \langle l_e \rangle (1 - T_I \langle m_e \rangle)]}{\Delta'} \\ \langle s_{NI} \rangle &= T_N \langle j \rangle \frac{T_I \frac{\langle jk \rangle}{\langle j \rangle} [1 - T_I(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta'} \\ &+ T_I \langle k \rangle \frac{(1 - T_N \langle j_e \rangle)[1 - T_I(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta'} \\ \langle s_{IN} \rangle &= T_N \langle l \rangle \frac{[1 - T_N(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})](1 - T_I \langle m_e \rangle)}{-\Delta'} \\ &+ T_I \langle m \rangle \frac{[1 - T_N(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})](-T_N \frac{\langle lm \rangle}{\langle m \rangle})}{\Delta'} \\ \langle s_{II} \rangle &= 1 + T_N \langle l \rangle \frac{[1 - T_N(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})]T_I \frac{\langle jk \rangle}{\langle j \rangle} [1 - T_I(\langle m_e \rangle - \frac{\langle lm \rangle}{\langle l \rangle})]}{\Delta'} \\ &+ T_I \langle m \rangle \frac{(1 - T_N \langle j_e \rangle)}{\Delta'} \\ &+ T_I \langle m \rangle \frac{T_I \frac{\langle jk \rangle}{\langle j \rangle} \left[-T_N(\langle l_e \rangle + \frac{\langle lm \rangle}{\langle m \rangle})(1 - T_N(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle})) \right]}{\Delta'} \end{aligned}$$

These diverge when $\Delta' = 0$.

$$\begin{aligned} 0 &= \Delta' \\ 0 &= \left[\frac{\langle jk \rangle}{\langle j \rangle} (\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle}) (\frac{\langle lm \rangle^2}{\langle l \rangle \langle m \rangle} - \langle l_e \rangle \langle m_e \rangle) \right] T_N^2 T_I^2 \\ &- \left[\frac{\langle jk \rangle}{\langle j \rangle} \left(\frac{\langle lm \rangle^2}{\langle l \rangle \langle m \rangle} + \langle l_e \rangle \langle m_e \rangle \right) \right] T_N T_I^2 \\ &+ \left[\frac{\langle jk \rangle}{\langle j \rangle} \langle l_e \rangle \left(\langle j_e \rangle - \frac{\langle jk \rangle}{\langle k \rangle} \right) \right] T_N^2 T_I \\ &+ \left(\frac{\langle jk \rangle}{\langle j \rangle} \langle l_e \rangle + \langle j_e \rangle \langle m_e \rangle \right) T_N T_I \\ &- \langle j_e \rangle T_N - \langle m_e \rangle T_I + 1 \end{aligned}$$

4.5 A Simple Case

To test the validity of this model, we will look at the simple case when the immunization provides complete immunity to the patient. That is when $T_I = 0$. We will keep with the simplifying assumption above that $T_{IN} = T_{NN} = T_N$ and $T_{NI} = T_{II} = T_I$. In this case, the occupied degree distributions are

$$\begin{aligned} F_0(x, y; T_N, 0) &= F_0(1 + (x - 1)T_N, 1) \\ &= \sum_{j=0}^{\infty} \sum_{k=0}^{\infty} p_{jk} [1 + (x - 1)T_N]^j \\ &= \sum_{j=0}^{\infty} p_j [1 + (x - 1)T_N]^j \end{aligned}$$

Similarly,

$$F_1^N(x, y; T_N, 0) = F_1^N(1 + (x - 1)T_N, 1).$$

We need not consider the excess occupied treated degree distribution for naive nodes because no immunized individual will cause an infection. We can also disregard the degree distributions for immunized people because they will neither get infected nor infect anyone else.

4.5.1 Outbreak Size

We only need to consider the size of an infected cluster connected to a naive node, so we need only deal with $H_0^N(x, y; \mathbf{T})$. Also, because no treated individuals will become infected,

$$\begin{aligned} H_0^N(x, y; \mathbf{T}) &= \sum_s P_s(\mathbf{T}) x^s y^0 \\ &= \sum_s P_s(\mathbf{T}) x^s \\ &= H_0^N(x, 1; \mathbf{T}) \end{aligned}$$

Then, we consider the size of a disease cluster extending from a naive-naive edge (the only occupied edges in this case). Thus,

$$H_1^{NN}(x, y; \mathbf{T}) = x F_1^N(H_1^{NN}(x, 1; \mathbf{T}), 1; \mathbf{T}).$$

Then,

$$H_0^N(x, 1; \mathbf{T}) = x F_0(H_1^{NN}(x, 1; \mathbf{T}), 1; \mathbf{T}),$$

and the average size of a naive cluster attached to a naive node is

$$\begin{aligned}
\langle s_{NN} \rangle &= \left. \frac{\partial H_0^N(x, 1; \mathbf{T})}{\partial x} \right|_{x=1} \\
&= 1 + \left. \frac{\partial F_0(H_1^{NN}(x, 1; \mathbf{T}), 1; \mathbf{T})}{\partial x} \right|_{x=1} \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1} \\
&= 1 + T_N \langle j \rangle \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1}
\end{aligned}$$

where

$$\begin{aligned}
\left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1} &= 1 + \left. \frac{\partial F_1^N(H_1^{NN}(x, 1; \mathbf{T}), 1; \mathbf{T})}{\partial x} \right|_{x=1} \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1} \\
&= \frac{1}{1 - T_N \langle j_e \rangle}
\end{aligned}$$

Thus,

$$\langle s_{NN} \rangle = 1 + \frac{T_N \langle j \rangle}{1 - T_N \langle j_e \rangle}$$

In this case, the critical transmissibility occurs when

$$T_N = \frac{1}{\langle j_e \rangle}$$

Above that, the probability that a large-scale epidemic will occur is

$$\begin{aligned}
S_N(T_N) &= 1 - H_0^N(1, 1; \mathbf{T}) \\
&= 1 - F_0(u, 1; \mathbf{T})
\end{aligned}$$

where u is the solution to

$$u = F_1^N(u, 1; \mathbf{T})$$

These equations align with the Newman model completely.

Chapter 5

Discussion

5.1 Overview

Two projects were completed in this thesis. In the first, we analyzed the predictions made by a contact network model for the spread of a mutating pathogen and compared those predictions to computer simulations that approximated the assumptions of the model. These comparisons showed that model does not accurately predict the size of an epidemic (either wild-type or mutant) but it does accurately predict the probability of a wild-type epidemic. In the second part, we developed a new model of disease spreading over a two-type contact network. Under certain conditions, we see that the model on the two-type network reduces to the simple contact network model.

5.2 Predictions of the Mutating Model

The graphs of $\langle s_w \rangle$, S_w and S_m with respect to T , show that the model is similar to that put forth by Newman, at least for the predicted wild-type values. We see that $\langle s_w \rangle$ behaves similarly to $\langle s \rangle$ with respect to the critical transmissibility values for the three types of networks. We also see that S_w behaves similarly to its counterpart in the basic model. Furthermore, S_m (Figure 6) exhibits some interesting logistic-type behavior for the Poisson and Exponential networks. The graph of S_m is concave up for these two types of networks until a value that appears to be close to each network types T^c value.

5.3 Simulations

As a result of running the simulations, we see several interesting things. First, figures 7-12 show how the proportion of each type of epidemic changes as a function of T . The proportion of wild-type infections overtakes the proportion of mutant infections at about the point where $T > T_\mu$. Figures 13-15 show that S_w accurately predicts the probability of a wild-type epidemic, at least for the given parameters. Furthermore, we see from figures 16-18 that S_m does not accurately predict the probability of a mutant epidemic above T_μ . Lastly, unlike the simple model, $S_w(T, \mu)$ and $S_m(T_\mu)$, the probabilities of epidemics emanating from each type of node in the mutating model, are not the same as the sizes of the epidemics.

5.4 Naive-Treated Derivations

In the special case of the model of disease spread on the two-type network with $T_I = 0$, the equations of the model reduce to equations similar to the basic model. The only exception is that there are still immunized individuals in the population, they are just immune to the disease.

5.5 Conclusions

The next step with this work is to determine if there is a way to approximate the size of a large-scale outbreak given the parameters of the model. Future simulations will account for the amount of *interference*, the failure of an infected node to infect a neighbor because the neighbor has already been infected. Determining the amount of interference will help determine if there is a way to approximate the size of a large-scale epidemic using the model.

From there, we will combine the the two parts of this thesis to study the spread of a mutating pathogen on a two-type network. This will allow us to study the effects of different treatment strategies on extent of an epidemic in order to find the optimal one. This could be quite useful with the threat of Avian Flu pandemic. Furthermore, combining these results could allow us to study the effects prophylactic treatment has on mutating disease. With the rise of antibiotic resistance in bacteria, this work could help model both the spread of antibiotic resistance genes through a bacteria population via conjugation or of a resistant pathogen through a network.

Appendix A

Pathogen Evolution Derivations

$$H_1^W(x; T, \mu) = xG_1^W(H_1^W(x; T, \mu), 1; T, \mu)$$

$$\begin{aligned} \frac{dH_1^W(x; T, \mu)}{dx} &= G_1^W(H_1^W(x; T, \mu), 1; T, \mu) \\ &\quad + x \frac{dG_1^W(H_1^W(x; T, \mu), 1; T, \mu)}{dx} \frac{dH_1^W(x; T, \mu)}{dx} \end{aligned}$$

$$\begin{aligned} \left. \frac{dH_1^W(x; T, \mu)}{dx} \right|_{x=1, y=1} &= G_1^W(H_1^W(1; T, \mu), 1; T, \mu) \\ &\quad + \left. \frac{dG_1^W(H_1^W(x; T, \mu), 1; T, \mu)}{dx} \right|_{x=1, y=1} \left. \frac{dH_1^W(x; T, \mu), 1; T, \mu)}{dx} \right|_{x=1, y=1} \\ &= 1 + G_1'(1)T(1 - \mu) \left. \frac{dH_1^W(x; T, \mu)}{dx} \right|_{x=1, y=1} \\ &= \frac{1}{1 - G_1'(1)T(1 - \mu)} \end{aligned}$$

$$\Gamma_1^M(x; T_\mu) = xG_1^M(\Gamma_1^M(x; T_\mu); T_\mu)$$

$$\frac{d\Gamma_1^M(x; T_\mu)}{dx} = G_1^M(\Gamma_1^M(x; T_\mu); T_\mu) + x \frac{dG_1^M(\Gamma_1^M(x; T_\mu); T_\mu)}{dx} \frac{d\Gamma_1^M(x; T_\mu)}{dx}$$

$$\begin{aligned} \left. \frac{d\Gamma_1^M(x; T_\mu)}{dx} \right|_{x=1} &= G_1^M(\Gamma_1^M(1; T_\mu); T_\mu) + \left. \frac{dG_1^M(\Gamma_1^M(x; T_\mu); T_\mu)}{dx} \right|_{x=1} \left. \frac{d\Gamma_1^M(x; T_\mu)}{dx} \right|_{x=1} \\ &= 1 + T_\mu G_1'(1) \left. \frac{d\Gamma_1^M(x; T_\mu)}{dx} \right|_{x=1} \\ &= \frac{1}{1 - G_1'(1)T_\mu} \end{aligned}$$

$$H_1^M(y; T, \mu, T_\mu) = G_1^W(H_1^M(y; T, \mu, T_\mu), \Gamma(y; T_\mu); T, \mu, T_\mu)$$

$$\begin{aligned} \frac{dH_1^M(y; T, \mu, T_\mu)}{dy} &= \frac{\partial G_1^W(H_1^M(y; T, \mu, T_\mu), \Gamma_1^M(y; T_\mu); T, \mu, T_\mu)}{\partial x} \frac{dH_1^M(y; T, \mu, T_\mu)}{dy} \\ &\quad + \frac{\partial G_1^W(H_1^M(y; T, \mu, T_\mu), \Gamma_1^M(y; T_\mu); T, \mu, T_\mu)}{\partial y} \frac{d\Gamma_1^M(y; T_\mu)}{dy} \end{aligned}$$

$$\begin{aligned} \left. \frac{dH_1^M(y; T, \mu, T_\mu)}{dy} \right|_{y=1} &= \left. \frac{\partial G_1^W(H_1^M(y; T, \mu, T_\mu), \Gamma_1^M(y; T_\mu); T, \mu, T_\mu)}{\partial x} \right|_{y=1} \left. \frac{dH_1^M(y; T, \mu, T_\mu)}{dy} \right|_{y=1} \\ &\quad + \left. \frac{\partial G_1^W(H_1^M(y; T, \mu, T_\mu), \Gamma_1^M(y; T_\mu); T, \mu, T_\mu)}{\partial y} \right|_{y=1} \left. \frac{d\Gamma_1^M(y; T_\mu)}{dy} \right|_{y=1} \\ &= T(1 - \mu)G_1'(1) \left. \frac{dH_1^M(y; T, \mu, T_\mu)}{dy} \right|_{y=1} + \frac{T\mu G_1'(1)}{1 - G_1'(1)T_\mu} \\ &= \frac{T\mu G_1'(1)}{(1 - G_1'(1)T_\mu)(1 - T(1 - \mu)G_1'(1))} \end{aligned}$$

Appendix B

Simulation Code

Below is the MatLab code used to simulate an epidemic on a Poisson network.

```
function [Num_Infected_Wildtype, Num_Infected_Mutant, Interference_Array] =  
MutatedPoissonSimulation(T, T_mu, mu)  
  
%MutatedPoissonSimulation simulates a mutating epidemic spreading through  
%a Poisson network for the parameters T, T_mu, and mu.  
  
load Network_Poi_clust_500_5_p0_1  
  
Start_Node = ceil(500*rand);  
Wildtype_Infected_Vector = Start_Node;  
Mutant_Infected_Vector = [];  
  
Susceptible = ones(1,500);  
Susceptible(Start_Node) = 0;  
  
Num_Infected_Wildtype = 1;  
Num_Infected_Mutant = 0;  
  
while(isempty(Wildtype_Infected_Vector)==0||isempty(Mutant_Infected_Vector)==0)  
  
if isempty(Wildtype_Infected_Vector) == 0  
Wildtype_Infected_Neighbors = [Network(Wildtype_Infected_Vector(1)).Neighbors];  
L = length(Wildtype_Infected_Neighbors);  
  
for i = 1:L  
r = random('unif',0,1);
```

```

    Neighbor = Wildtype_Infected_Neighbors(i);
    if r < T*Susceptible(Neighbor)
        r_mu = random('unif',0,1);
    if r_mu < mu
        Mutant_Infected_Vector = horzcat(Mutant_Infected_Vector, Neighbor);
        Num_Infected_Wildtype = Num_Infected_Wildtype + 1;
    else
        Wildtype_Infected_Vector = horzcat(Wildtype_Infected_Vector, Neighbor);
        Num_Infected_Wildtype = Num_Infected_Wildtype + 1;
    end

    Susceptible(Neighbor) = 0;
end
Wildtype_Infected_Vector(1) = [];
end

if isempty(Mutant_Infected_Vector) == 0
    Mutant_Infected_Neighbors = [Network(Mutant_Infected_Vector(1)).Neighbors];
    L_mu = length(Mutant_Infected_Neighbors);

    for i = 1:L_mu
        r = random('unif',0,1);
        Neighbor = Mutant_Infected_Neighbors(i);

        if r < T_mu*Susceptible(Neighbor)
            Mutant_Infected_Vector = horzcat(Mutant_Infected_Vector, Neighbor);
            Susceptible(Neighbor) = 0;
            Num_Infected_Mutant = Num_Infected_Mutant + 1;
        end
        Mutant_Infected_Vector(1) = [];
    end
end
end

```

Appendix C

Derivations for Naive-Treated Dynamics

C.1 Finding $\langle s_{NN} \rangle$

$$\langle s_{NN} \rangle = \left. \frac{\partial H_0^N(x, y; \mathbf{T})}{\partial x} \right|_{x=1, y=1}$$

$$\begin{aligned} \frac{\partial H_0^N(x, y; \mathbf{T})}{\partial x} &= F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}) + \\ &\quad x \left[\frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{NN}}{\partial x} \right] + \\ &\quad x \left[\frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{NI}}{\partial x} \right] \\ &= F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}) \\ &\quad + x \left[T_{NN} \langle j \rangle F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{NN}}{\partial x} \right] \\ &\quad + x \left[T_{NI} \langle k \rangle F_1^I(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{NI}}{\partial x} \right] \end{aligned}$$

$$\begin{aligned}
\langle s_{NN} \rangle &= \left. \frac{\partial H_0^N}{\partial x} \right|_{x=1, y=1} \\
&= F_0(H_1^{NN}(1, 1; \mathbf{T}), H_1^{NI}(1, 1; \mathbf{T}); \mathbf{T}) \\
&\quad + \left[\left. \frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} \right] \\
&\quad + \left[\left. \frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1} \right] \\
&= 1 + \left[T_{NN} \langle j \rangle \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} + T_{NI} \langle k \rangle \left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1} \right]
\end{aligned}$$

C.2 Finding $\langle s_{NI} \rangle$

$$\langle s_{NI} \rangle = \left. \frac{\partial H_0^N(x, y; \mathbf{T})}{\partial y} \right|_{x=1, y=1}$$

$$\begin{aligned}
\frac{\partial H_0^N(x, y; \mathbf{T})}{\partial y} &= x \left[\frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{NN}}{\partial y} \right] \\
&\quad + x \left[\frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{NI}}{\partial y} \right] \\
&= x \left[T_{NN} \langle j \rangle F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{NN}}{\partial y} \right] \\
&\quad + x \left[T_{NI} \langle k \rangle F_1^I(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{NI}}{\partial y} \right]
\end{aligned}$$

$$\begin{aligned}
\langle s_{NI} \rangle &= \left. \frac{\partial H_0^N}{\partial y} \right|_{x=1, y=1} \\
&= \left[\left. \frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NN}}{\partial y} \right|_{x=1, y=1} \right] + \\
&\quad \left[\left. \frac{\partial F_0(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NI}}{\partial y} \right|_{x=1, y=1} \right] \\
&= \left[T_{NN} \langle j \rangle \left. \frac{\partial H_1^{NN}}{\partial y} \right|_{x=1, y=1} + T_{NI} \langle k \rangle \left. \frac{\partial H_1^{NI}}{\partial y} \right|_{x=1, y=1} \right]
\end{aligned}$$

C.3 Finding $\langle s_{IN} \rangle$

$$\langle s_{IN} \rangle = \left. \frac{\partial H_0^I(x, y; \mathbf{T})}{\partial x} \right|_{x=1, y=1}$$

$$\begin{aligned} \frac{\partial H_0^I(x, y; \mathbf{T})}{\partial x} &= y \left[\frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{IN}}{\partial x} \right] \\ &\quad + y \left[\frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{II}}{\partial x} \right] \\ &= y \left[T_{IN} \langle l \rangle G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{IN}}{\partial x} \right] \\ &\quad + y \left[T_{II} \langle m \rangle G_1^I(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{II}}{\partial x} \right] \end{aligned}$$

$$\begin{aligned} \langle s_{IN} \rangle &= \left. \frac{\partial H_0^I}{\partial x} \right|_{x=1, y=1} \\ &= \left[\left. \frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{IN}}{\partial x} \right|_{x=1, y=1} \right] \\ &\quad + \left[\left. \frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{II}}{\partial x} \right|_{x=1, y=1} \right] \\ &= 1 + \left[T_{IN} \langle l \rangle \left. \frac{\partial H_1^{IN}}{\partial x} \right|_{x=1, y=1} + T_{II} \langle m \rangle \left. \frac{\partial H_1^{II}}{\partial x} \right|_{x=1, y=1} \right] \end{aligned}$$

C.4 Finding $\langle s_{II} \rangle$

$$\langle s_{II} \rangle = \left. \frac{\partial H_0^I(x, y; \mathbf{T})}{\partial x} \right|_{x=1, y=1}$$

$$\begin{aligned}
\frac{\partial H_0^I(x, y; \mathbf{T})}{\partial y} &= G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}) + \\
&+ y \left[\frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{IN}}{\partial y} \right] \\
&+ y \left[\frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{II}}{\partial y} \right] \\
&= G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}) \\
&+ y \left[T_{IN} < l > G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{IN}}{\partial y} \right] \\
&+ y \left[T_{II} < m > G_1^I(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T}) \frac{\partial H_1^{II}}{\partial y} \right]
\end{aligned}$$

$$\begin{aligned}
< s_{II} > &= \left. \frac{\partial H_0^N}{\partial y} \right|_{x=1, y=1} \\
&= G_0(H_1^{IN}(1, 1; \mathbf{T}), H_1^{II}(1, 1; \mathbf{T}); \mathbf{T}) \\
&+ \left. \frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{IN}}{\partial y} \right|_{x=1, y=1} \\
&+ \left. \frac{\partial G_0(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{II}}{\partial y} \right|_{x=1, y=1} \\
&= 1 + \left[T_{IN} < l > \left. \frac{\partial H_1^{IN}}{\partial y} \right|_{x=1, y=1} + T_{II} < m > \left. \frac{\partial H_1^{II}}{\partial y} \right|_{x=1, y=1} \right]
\end{aligned}$$

C.5 Partial Derivatives of H_1^{jk}

$$\begin{aligned}
\frac{\partial H_1^{NN}}{\partial x} &= F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T}) + \\
&x \left[\frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{NN}}{\partial x} \right] \\
&+ x \left[\frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{NI}}{\partial x} \right]
\end{aligned}$$

$$\begin{aligned}
\left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} &= F_1^N(H_1^{NN}(1, 1; \mathbf{T})(H_1^{NI}(1, 1; \mathbf{T}); \mathbf{T}) \\
&+ \left. \frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} \\
&+ \left. \frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1} \\
&1 + T_{NN} < j_e > \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} + T_{NI} \frac{< jk >}{< j >} \left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1}
\end{aligned}$$

$$\begin{aligned}
\frac{\partial H_1^{NN}}{\partial y} &= x \left[\frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{NN}}{\partial y} \right] \\
&+ x \left[\frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{NI}}{\partial y} \right]
\end{aligned}$$

$$\begin{aligned}
\left. \frac{\partial H_1^{NN}}{\partial y} \right|_{x=1, y=1} &= \left. \frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} \\
&+ \left. \frac{\partial F_1^N(H_1^{NN}(x, y; \mathbf{T}), H_1^{NI}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{NI}}{\partial y} \right|_{x=1, y=1} \\
&T_{NN} < j_e > \left. \frac{\partial H_1^{NN}}{\partial x} \right|_{x=1, y=1} + T_{NI} \frac{< jk >}{< j >} \left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1}
\end{aligned}$$

$$H_1^{NI}(x, y; \mathbf{T}) = y G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})$$

$$\begin{aligned}
\frac{\partial H_1^{NI}}{\partial x} &= y \left[\frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{IN}}{\partial x} \right] \\
&+ y \left[\frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{II}}{\partial x} \right]
\end{aligned}$$

$$\begin{aligned}
\left. \frac{\partial H_1^{NI}}{\partial x} \right|_{x=1, y=1} &= \left. \frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{IN}}{\partial x} \right|_{x=1, y=1} \\
&+ \left. \frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{II}}{\partial x} \right|_{x=1, y=1} \\
&= T_{IN} < l_e > \left. \frac{\partial H_1^{IN}}{\partial x} \right|_{x=1, y=1} + T_{II} \frac{< lm >}{< l >} \left. \frac{\partial H_1^{II}}{\partial x} \right|_{x=1, y=1}
\end{aligned}$$

$$\begin{aligned}\frac{\partial H_1^{NI}}{\partial y} &= y \left[\frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \frac{\partial H_1^{IN}}{\partial y} \right] \\ &+ y \left[\frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \frac{\partial H_1^{II}}{\partial y} \right]\end{aligned}$$

$$\begin{aligned}\left. \frac{\partial H_1^{NI}}{\partial y} \right|_{x=1, y=1} &= \left. \frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial x} \right|_{x=1, y=1} \left. \frac{\partial H_1^{IN}}{\partial y} \right|_{x=1, y=1} \\ &+ \left. \frac{\partial G_1^N(H_1^{IN}(x, y; \mathbf{T}), H_1^{II}(x, y; \mathbf{T}); \mathbf{T})}{\partial y} \right|_{x=1, y=1} \left. \frac{\partial H_1^{II}}{\partial x} \right|_{x=1, y=1} \\ &= T_{IN} \langle l_e \rangle \left. \frac{\partial H_1^{IN}}{\partial y} \right|_{x=1, y=1} + T_{II} \frac{\langle lm \rangle}{\langle l \rangle} \left. \frac{\partial H_1^{II}}{\partial y} \right|_{x=1, y=1}\end{aligned}$$

Now we have systems of equations for the partial derivatives of H_1^{NN} , H_1^{NI} , H_1^{IN} , and H_1^{II} evaluated at $x = 1$, $y = 1$.

$$\mathbf{A}\vec{x} = \vec{b} \text{ and } \mathbf{A}\vec{y} = \vec{c}$$

where

$$\mathbf{A} = \begin{bmatrix} 1 - T_{NN} \langle j_e \rangle & -T_{NI} \left(\frac{\langle jk \rangle}{\langle j \rangle} \right) & 0 & 0 \\ 0 & 1 & -T_{IN} \langle l_e \rangle & -T_{II} \left(\frac{\langle lm \rangle}{\langle l \rangle} \right) \\ -T_{NN} \left(\frac{\langle jk \rangle}{\langle k \rangle} \right) & -T_{NI} \langle k_e \rangle & 1 & 0 \\ 0 & 0 & -T_{IN} \left(\frac{\langle lm \rangle}{\langle m \rangle} \right) & 1 - T_{II} \langle m_e \rangle \end{bmatrix}$$

$$\vec{x} = \left[\begin{array}{c} \frac{\partial H_1^{NN}}{\partial x} \\ \frac{\partial H_1^{NI}}{\partial x} \\ \frac{\partial H_1^{IN}}{\partial x} \\ \frac{\partial H_1^{II}}{\partial x} \end{array} \right]_{x=1, y=1} \quad \vec{b} = \left[\begin{array}{c} 1 \\ 0 \\ 1 \\ 0 \end{array} \right]$$

$$\vec{y} = \left[\begin{array}{c} \frac{\partial H_1^{NN}}{\partial y} \\ \frac{\partial H_1^{NI}}{\partial y} \\ \frac{\partial H_1^{IN}}{\partial y} \\ \frac{\partial H_1^{II}}{\partial y} \end{array} \right]_{x=1, y=1} \quad \vec{c} = \left[\begin{array}{c} 0 \\ 1 \\ 0 \\ 1 \end{array} \right]$$

Appendix D

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